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DIAGNOSIS OF CONGENITAL CYSTIC DISEASE OF THE LUNG

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BROOKLYN

During the past few years the condition described as congenital cystic disease of the lung has attracted considerable attention. No longer accidentally observed at necropsy, the lesion is recognized during life, and in a number of cases it can be successfully treated. Synonymous terms, such as fetal bronchiectasis, congenital bronchiectasis, atelectatic bronchiectasis and congenital pulmonary lymphangiectasis, have been replaced by the more proper designation, namely, congenital cystic disease of the lung.

Responsible for initiating the recent interest in this condition was Koontz,¹ who reviewed the literature in 1925 and collected reports of 108 proved cases. In a recent communication (1936) I² reported from the world's literature an additional 124 cases and 4 original cases, making a total of 236 cases of congenital cystic disease of the lung on record. Since the writing of my last paper, or in the past year and a half, 140 additional reports of cases have been collected. Including the 5 new cases to be described, the grand total is brought up to 381 cases noted since Bartholinus³ recorded the first case in 1687.

Regarding the lung as a frequent seat of congenital anomalies, Sauerbruch⁴ said he believed that cystic disease is not a rare clinical entity, though it is little appreciated by pediatricians. Having treated many patients by surgical removal of the cystic lesion, he was of the opinion that in over 80 per cent of the cases bronchiectasis in children limited to one lobe is of congenital origin. In the fifty-eight lobes which he resected he found no evidence of inflammatory pulmonary changes.

From the Department of Radiology, the Jewish Hospital

1 Koontz, A. R. Congenital Cysts of the Lung, *Bull Johns Hopkins Hosp* **37**:340-361, 1925

2 Schenck, S. G. Congenital Cystic Disease of the Lungs, *Am J Roentgenol* **35** 604-629 (May) 1936

3 Bartholinus, T., in Malpighi, M. *Opera omnia*, London, R. Littlebury, 1687, pp 349-350

4 Sauerbruch, F. Die operative Behandlung der kongenitalen Bronchiektasen, *Arch f klin Chir* **180** 312-320, 1934

or pleural adhesions, the alterations consisting of cystic bronchial disease and thickening of the pulmonary tissue. Another point of evidence is the absence of a history of colds, influenza and pneumonia.

CLASSIFICATION

Congenital cystic disease of the lung is a developmental malformation which may involve any portion of the bronchial tree or interstitial pulmonary tissue, forming single or multiple discrete cells or pouches. The cysts may be so numerous and small as to give the lobe or lung a honeycomb appearance, or there may be only a solitary sac, which may occupy the entire hemithorax and may even encroach on the heart and mediastinal structures.

Cysts are solitary or multiple (table 1) and contain a milky or turbid fluid at birth. Their fluid contents persist, provided they do not rupture into a neighboring bronchus or bronchiole. If rupture ensues,

TABLE 1—*Modification of the Anspach and Wolman* Classification of Congenital Pulmonary Cysts*

A Solitary fluid cyst (at birth)			
1	With no bronchial communication	→	Solitary fluid cyst
2	With bronchial communication	→	Solitary air cyst
	a With free opening	→	Nonexpansile air cyst
	b With one way mechanism at orifice	→	Expansile air cyst
B Multiple fluid cysts (at birth)			
1	With no bronchial communication	→	Multiple fluid cysts
2	With bronchial communication	→	Multiple or trabeculated air cysts
	a With free opening	→	Nonexpansile or trabeculated air cysts
	b With one way valve mechanism at orifice	→	Expansile or trabeculated air cysts

* This classification has been explained by Anspach and Wolman in detail (Surg., Gynec. & Obst. 56: 635-645, 1933).

air replaces the fluid, and the lesion is designated as a solitary air cyst or as multiple or trabeculated air cysts, as the case may be. If the communicating channel between the cystic cavity and the bronchus is patent during inspiration and expiration, allowing the free passage of air in both directions, the cyst remains stationary in size or nonexpansile. However, should the air become trapped within the cystic space, owing to a valvelike action at the orifice, so that the air enters the cyst but its outflow is obstructed during expiration, the cyst "balloons" out, or becomes expansile. The same mechanism obtains with multiple or trabeculated cysts.

In the 374 cases in which mention was made of the type of cyst found, there were 141 solitary, or single, cysts, the remaining 233 being multiple (table 2). The right lung alone was involved in 157 cases (42

per cent) and the left in 136 (37 per cent), in 78 (21 per cent) the lesion was bilateral

PATHOLOGIC PICTURE

The precise pathogenesis of cystic disease of the lung is unknown, though the opinion prevails that the lesion is a congenital anomaly or malformation caused by a pinching off of a small pulmonary bud, which continues to develop into pulmonary tissue. The retained secretions, apparently of mucosal origin, having no bronchial outlet, distend the enclosed space, which encroaches on and compresses the surrounding alveoli. The wall of the cyst is usually made up of high or low columnar epithelium, with or without cilia, muscle and elastic tissue, and cartilage, sporadically arranged, a picture which points to a bronchial origin. The absence of anthracotic pigment within and in the vicinity of the wall of the cyst indicates the functionless nature of the tissue and its congenital origin.

TABLE 2—*Incidence of the Types of Cysts*

	Infants and Children	Adults	Total
Solitary Cysts			
Fluid cyst	28	21	49
Air (nonexpansile) cyst	22	33	55
Balloon (expansile) cyst	22	5	37
Total number of cases of solitary cysts	82	59	141
Multiple Cysts			
Fluid cysts	25	13	38
Air (nonexpansile) cysts	50	138	188
Balloon (expansile) cysts	5	2	7
Total number of cases of multiple cysts	80	153	233

In 45 cases in which necropsy was performed, other congenital abnormalities were noted besides the cystic malformation of the lung. The most frequent anomaly was some pulmonary defect, as an accessory lobe or lung, which not infrequently harbored the cystic defect.

SYMPTOMS

The diagnosis is dependent chiefly on the roentgenographic findings, aided by a painstaking study of the history. With symptoms present since birth or shortly thereafter, in the absence of a history of severe disease of the respiratory tract, and with the roentgenographic evidence of a gross pulmonary pathologic condition of the type to be described, the diagnosis of the congenital lesion is in most cases not difficult. The more prominent symptoms (table 3), especially in infants and children, are recurring attacks of dyspnea and cyanosis,⁵ with or without cough.

5 Morgan, E. A., and Brown, A. Cyanosis of the New-Born, *J. A. M. A.* 105: 1085-1088 (Oct. 5) 1935. It is of interest to note that Morgan and Brown failed to mention congenital cystic disease of the lung in their classification of the causes of cyanosis of the new-born.

These attacks may be so mild as to be overlooked or may assume such serious proportions as to cause fear of terminating fatally. Dyspnea and cyanosis are most prominent in the expansile air cysts and may not be relieved until the cyst is punctured and the trapped air withdrawn or until the cyst is deflated by rupture into the pleural space, resulting in a partial pneumothorax, or is emptied when the valvelike obstruction at its bronchial orifice is removed.

Expectoration is dependent on the presence of a channel between the cyst and the bronchus. With such a communication the cystic contents are often infected, and the symptoms are not unlike bronchiectasis from contractive causes. The elevation in temperature, which is seldom great, is dependent on the presence or absence of infection. Another important symptom which is by no means uncommon is

TABLE 3—*Frequency of the More Common Symptoms*

	Infants and Children	Adults	Total
Cough	76	141	217
Dyspnea	76	78	154
Expectoration	40	112	152
Cyanosis	52	23	75
Fever	28	44	72
Hemoptysis	5	47	52
Malnutrition	29	21	50
Thoracic pain	6	33	39
Weakness	10	23	33
Anorexia	14	6	20
Wheezing	11	8	19
Vomiting	16	1	17
Palpitation	1	11	12
Epigastric distress		7	7

hemoptysis, which may be slight and may result in the expectoration of blood-streaked sputum or of frank blood. Many of these patients have been needlessly treated for tuberculosis because of the bloody expectoration and the roentgenographic finding of a cavity in the upper lobe of a lung, notwithstanding the sputum has persistently failed to show tubercle bacilli. Pains in the chest may or may not be present. Among the less frequent symptoms may be mentioned weakness, anorexia, palpitation and vomiting, particularly in children. Occasionally the distress from an intrathoracic lesion is referred to the epigastrium. This referred pain may mislead the clinician at first, and this possibility must be borne in mind. The symptoms of dyspnea and cough, sometimes with pronounced wheezing, present in 19 cases in this series, may suggest a diagnosis of asthma and for a time may overshadow the underlying pathologic condition.

The physical signs are seldom definite but not infrequently indicate the presence of a pulmonary lesion. The signs naturally vary with the size and number of cysts and the nature of their contents (air or

fluid) Other congenital malformations are sometimes present In a number of cases the cystic lesion in the lung is a purely accidental finding, no symptom or signs being presented The discovery may be at birth or soon thereafter, or the lesion may escape detection until death occurs as a result of other causes and is revealed at necropsy (table 4) Not infrequently (18 cases) the condition is accidentally found during a roentgenographic examination for some other malady

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

The diagnosis frequently rests on a painstaking roentgenologic examination, which includes anteroposterior and lateral views as well as a careful roentgenoscopic study In rare instances stereoscopic films are necessary in order to furnish additional information

Not infrequently the roentgenograms portray extensive pathologic changes in a patient who appears comfortable and presents surprisingly few symptoms It is well to remember this point in arriving at a diagnosis of congenital pulmonary malformation

TABLE 4—*Age at Which Condition Was Recognized*

	Number of Cases
At birth	36
Under 1 yr	57
Between 1 and 15 yr	68
Over 15 yr	207
Total	368

A solitary fluid cyst is observed in the roentgenograms as a moderately dense, opaque, globular shadow which lies within the pulmonary parenchyma The density of the cystic shadow is slightly less than the opacity cast by the heart and often can be separated from the cardiac shadow in the lateral studies If there is an uncomplicated fluid cyst the aspirated specimen resembles amniotic fluid, appearing slightly milky or albuminous and moderately viscid Cultures show no growth, the microscopic study may reveal the presence of ciliated columnar epithelium and, occasionally, goblet cells The lesion must be differentiated from a solid tumor, acquired cystic disease and an inflammatory lesion

Among the solid tumors, malignant growth, teratoma, chondroma and ganglioneuroma may be mentioned Malignant disease is readily excluded by the history, physical examination and clinical course in each case A teratoma should offer little difficulty, because it originates in the mediastinal spaces and usually begins to develop after puberty Ganglioneuroma and chondroma may be more difficult to identify at first The fact that a solid tumor is more opaque roentgenographically and its outer border more sharply defined than the walls of a cyst, which has

rather poorly defined borders as compared with those of a tumor, will tend to differentiate the two conditions. Furthermore, a tumor has the tendency to grow, whereas a fluid cyst remains stationary for a long period. Lastly, if doubt still exists, puncture of the cyst and the obtaining of the characteristic fluid will decidedly exclude the presence of a solid tumor.

In acquired cystic disease the lesions that may simulate a congenital solitary fluid cyst are echinococcic, dermoid, hydatid and mediastinal cysts. An echinococcic cyst is excluded by the complement fixation test and by the presence of eosinophilia. Urticaria is not infrequently present and other lesions may be found. When the cyst ruptures into a bronchus, the characteristic hooklets in the sputum establish the diagnosis. A dermoid cyst is differentiated by the presence of bone or teeth in the roentgenograms or by the finding of hair or cartilage in the expectoration. Hydatid and mediastinal cysts are mediastinal in origin and usually produce little or no dyspnea. If rupture of a hydatid cyst occurs, the watery nature of the fluid is rather characteristic, and hooklets and fragments of membrane may be found in the sputum.

Inflammatory lesions are among the more common conditions that must be separated from a congenital solitary fluid cyst, and included among these acquired processes are pneumonia, localized fluid or encapsulated empyema, pulmonary abscess and an interlobar collection of fluid or pus. Pneumonia should offer no difficulty. When there is encapsulated fluid, the opacity is outside the lung, and the history of a recent infection is elicited. Furthermore, the patient appears acutely ill, and the temperature is "spiked," whereas the patient with cystic disease is often relatively comfortable. The history and the appearance of the patient may similarly exclude a diagnosis of interlobar fluid. The fluid usually appears on the roentgenogram as a wedge-shaped opacity taking the direction of the interlobar fissure. In separating pulmonary abscess from cystic disease the previous history and clinical course, the inconstant roentgenographic findings and the poorly defined borders, due to the surrounding pneumonitis, present in pulmonary suppuration tend to furnish little difficulty. Thoracentesis, with examination of the aspirated fluid, may be necessary to establish the diagnosis.

A solitary nonexpansile air cyst reveals a pocket of air that is intrapulmonary and usually globular or spherical. A moderately thin capsule or wall delimits the air space, which shows no pulmonary markings but may reveal fine linear strands traversing the cystic space in a slightly curving fashion indicative of trabeculations. Roentgenoscopically an increase in illumination within the cyst is often observed during forceful inspiration. This type of cyst must be separated from an emphysematous bulla, which shows no delimiting wall, from localized or partial pneumothorax and from a tuberculous cavity. In addition to

the fact that no wall surrounds the air pocket which lies outside of pulmonary parenchyma, localized pneumothorax appears irregular in contour and does not persist unchanged for a long period. On deep inspiration no increased illumination within the cystic space is noted roentgenoscopically. A tuberculous vomica may resemble a solitary air cyst, especially a cyst that is located in the upper lobe. However, the dense, broader walls and the concomitant pulmonary infiltration and changes observed in tuberculosis are absent in cystic disease. The fact that patients with cystic disease have been treated for tuberculosis indicates the necessity for the examiner to be cyst conscious if a proper separation of the two conditions is to be made.

In the expansile or balloon type of cyst, with increasing symptoms of dyspnea and cyanosis, the roentgenographic picture is rather unusual. There is an obliteration of the pulmonary markings, with air filling the entire hemithorax from apex to base. The findings are not unlike those of complete pneumothorax, from which it may not be so readily differentiated. The heart and mediastinal contents appear displaced to the normal side, and the diaphragmatic leaf on the affected side is depressed and flattened. A slight haziness is often noted in the apex, and the costophrenic angle is obliterated. These findings represent atelectatic pulmonary tissue due to the compression of the lung in all directions by the expanding cyst. Instead of the collapsed lung appearing as a broad stump at the root, as observed in cases of pneumothorax, the hilar shadow is narrow and elongated, owing to the fact that the expansile cyst is compressing the pulmonary tissue peripherally. The cystic wall can usually be detected, especially its mesial portion, overlapping part of the heart and encroaching on the mediastinum. The fine, slightly curved strands traversing the cystic space are often portrayed. In infants and children the affected side of the chest bulges and lags on respiration. Thoracentesis releases air under pressure. When there is an air cyst, the walls of which lack clarity or merge with the thoracic wall and are thus obscured, induced pneumothorax results in unusually clear roentgenograms which portray the cystic space lying within the partially collapsed lung. The air, artificially introduced into the pleural space, retracts the outer border of the lung and the cystic wall from the ribs. The contrast between the air in the pleural cavity and that in the cystic space with its surrounding capsule lying in the partially retracted lung establishes the diagnosis and differentiates a cystic condition from pneumothorax, either acquired or congenital.

Multiple air cysts (polycystic lung) are characterized by their sharply defined spherical cavities, discrete and irregularly arranged, and the lack of pulmonary infiltration between them. In these cases there is a paucity of clinical symptoms, unlike cases of acquired bronchiectasis, with which the condition may be confused. In the sacculated form of

bronchiectasis from contractive processes, the cavities are smaller, less discrete and more or less definitely arranged in relation to the affected bronchus or bronchi. In addition, there is roentgenographic evidence of secondary pulmonary changes around and between the cavities. Bronchiectasis often follows a severe respiratory infection, whereas the absence of such a history and the presence of more or less mild symptoms since birth or early childhood indicate the probability of an underlying congenital malformation. However, in some instances differentiation is impossible, and an absolute diagnosis must be deferred until necropsy reveals the absence of pigmentation in the walls of the cavities which would indicate their congenital origin.

When there are multiple air cysts, diaphragmatic hernia or eventration can readily be excluded by the absence of gurgling sounds on auscultation of the chest and by the intake of a barium meal.

TABLE 5—*Causes of Death*

	Infants and Children		Adults		Total	
	Number	Percent age	Number	Percent age	Number	Percent age
Congenital cystic disease	70	60.9	44	56.4	114	59.0
Pneumonia	26	22.6	7	9.0	33	17.0
Tuberculosis	2	1.7	3	3.8	5	2.7
Cardiac failure	2	1.7	3	3.8	5	2.7
Other causes	15	13.1	21	27.0	36	18.6
Total	115		78		193	

Occasionally, bronchoscopic examination and visualization of the bronchial tree with iodized poppy-seed oil 40 per cent may aid in the diagnosis. Although the presence of pus in the bronchus may not differentiate bronchiectasis from an infected cyst, nevertheless, the increased clarity of the cavity filled with iodized oil affords a better opportunity to separate the two conditions. When there is a fluid cyst with no bronchial connection, the opaque oil will fill the entire bronchial tree except for the region occupied by the fluid cyst. When there is a large air cyst, iodized oil may be introduced by thoracentesis under roentgenoscopic control. This procedure is feasible when the outer wall of the cyst lies in close approximation with the thoracic wall.

The visualization of the oil-filled cystic space aids materially in rendering a correct diagnosis.

PROGNOSIS AND TREATMENT

The prognosis and treatment of this congenital defect depend on the number, size, type and location of the cystic lesions, as well as on the age of the patient and the presence or absence of infection. Although the condition is not incompatible with long life, nevertheless the mortality is high among infants and children, especially those with the expansile type of cyst (table 5). Surgical extirpation of the cystic

defect or lobectomy is the only rational form of treatment in selected cases Sauerbruch,⁴ who performed fifty-eight lobectomies for congenital bronchiectasis, including two extirpations of the whole lung accomplished in two or more stages, with six deaths and fifty-one complete cures without a fistula, stated his conviction that the treatment of choice for a congenital malformation is extirpation of the involved lobe. This operation should be performed early, before the secondary alterations have time to develop. Edwards and Thomas,⁶ Flemming-Møller,⁷ Sultan,⁸ Eloesser,⁹ Harrington,¹⁰ Melchior¹¹ and others also have performed successful lobectomies on children as well as on adults.

Although the procedure is attended with grave dangers, the reduction in the mortality and morbidity in these operations offers hope and encouragement to these unfortunate patients.

REPORT OF CASES

The following reports of new cases are added to the 4 which I² have already published elsewhere.

CASE 1—R E, a full term infant, weighing 8 pounds and 10 ounces (4,000 Gm), was delivered by low forceps with no apparent injury. She was discharged from the hospital with her mother in twelve days in good condition, with no record of convulsions, cyanosis or snuffles. Shortly afterward the mother noticed that the infant "snorted" and made peculiar sounds when nursing. There were also several short "spells of heavy breathing." When 2 months old the infant had a mucopurulent nasal discharge, for which a physician prescribed nose drops. Immediately after their use, the child began to cough and gag. Although the drops were discontinued, the bouts of coughing and gagging, with occasional vomiting, persisted. There was a rise of temperature to 102 F for several days. The physician remarked that the child "looked like a thymus baby." The symptoms persisted for three weeks with more or less severity until the night prior to the infant's admission to the hospital, when she suddenly became markedly dyspneic and cyanotic, with a harassing unproductive cough.

When brought to the hospital, the infant appeared in a moribund condition. Cyanosis was pronounced, and she gasped for breath, utilizing all the accessory respiratory muscles. The eyes were staring, and the body was limp. She appeared to be a well nourished and well developed infant of 3 months. The

6 Edwards, A T, and Thomas, C P. One-Stage Lobectomy for Bronchiectasis. An Account of Forty-Eight Cases, *Brit J Surg* **22** 310-331, 1934.

7 Flemming-Møller, P. Congenital Thoracic Cysts and Lung Deformities in the Roentgen Picture, *Acta radiol* **9** 460-473, 1928.

8 Sultan, G. Bronchuscyste, *Zentralbl f Chir* **52** 869-873, 1925.

9 Eloesser, L. Congenital Cystic Disease of the Lung, *S Clin North America* **8** 1361-1373, 1928, *Surg, Gynec & Obst* **52** 747-758, 1931, *Radiology* **17** 912-929, 1931.

10 Harrington, S W. Surgical Treatment of Intrathoracic Tumors, *Arch Surg* **19** 1679-1725 (Dec) 1929.

11 Melchior, E. Zur Kenntnis der kongenitalen tracheobronchialen Cysten der Lunge, *Zentralbl f Chir* **56** 2626-2630, 1929.

anterior fontanel was opened but showed no bulging. The pupils were dilated and reacted poorly to light. The nose revealed a slight mucopurulent discharge, with evidence of mild congestion of the nasal and pharyngeal mucosa. The heart rate was rapid, and the sounds and rhythm were normal. The right lung was hyperresonant on percussion, and the breath sounds appeared distant or absent. Posteriorly, along the vertebral border, some fine râles and some bronchial breathing were heard. The left lung was normal except for a few scattered râles. No abnormal findings were observed on examination of the abdomen.

When admitted to the hospital the infant had a temperature of 101 F. The blood count showed 31,000 white blood cells. Roentgenographic examination (fig 1) revealed multiple large and small cystic areas that occupied the entire right side of the thorax, encroaching on the heart and mediastinal spaces, which

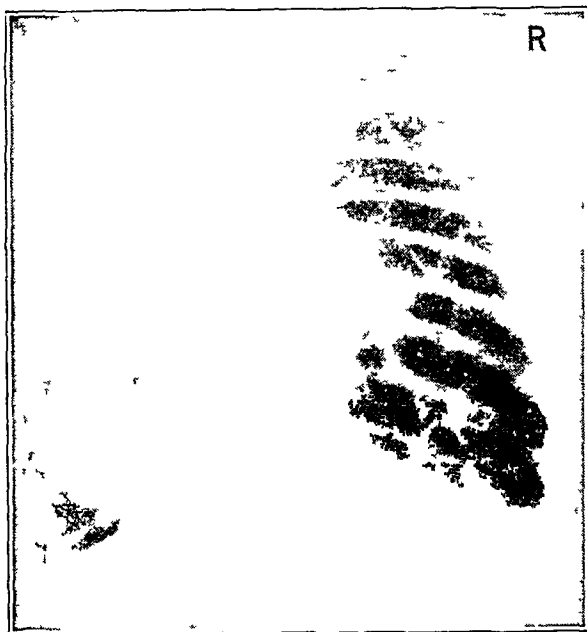


Fig 1 (case 1)—The right lung shows many large and small air cysts, the expansile nature of which is recognized by the displacement of the heart and mediastinal contents to the opposite side and the encroachment of the cystic spaces on the mediastinum and the left lung.

were decidedly shifted to the left. The cystic spaces contained air and presented thin but well formed walls. The lung was apparently crowded out in all directions, appearing compressed in the apex and at the base, especially in the costophrenic sinus. The upper border of the opacity at the costophrenic sinus and the right diaphragmatic cusp were concave, conforming to the pressure effect from the contiguous cysts. The borders of a large cyst were discernible overlying the mediastinum and the heart and encroaching considerably on the left lung. The roentgenographic findings were interpreted as indicating congenital multiple or trabeculated expansile cysts of the lung.

The infant was placed in an oxygen tank, and 100 cc of 5 per cent solution of dextrose was given intravenously. A needle was inserted into the right side of the chest posteriorly, and 30 cc of air was withdrawn under pressure. Following this procedure there was temporary relief from the dyspnea and cyanosis,

which returned to an alarming degree the same afternoon, accompanied with a rise in temperature to 106 F. Death occurred within twenty-four hours after the infant's admission to the hospital.

Gross Postmortem Examination—Only the lungs were obtained. What was considered to be the right lung (fig 2) consisted of a portion of tissue measuring 10.5 by 8 by 2.5 cm. The external surface was smooth and shiny, except over an area measuring 4 by 3 cm, where it appeared slightly roughened. The cut surfaces were entirely composed of cavities varying from 0.2 to 6 cm in diameter separated by delicate partitions. Some of the cavities communicated with each



Fig 2 (case 1)—Gross specimen of the right cystic lung, showing cavities of various sizes and practically no normal pulmonary tissue.

other by narrow openings. The internal surface of the cavities was glistening, dotted in places with red areas or traversed by delicate blood vessels. Accompanying this was a small portion of tissue from the left lung. Two sections from the left lung and one from the cystic structure were taken for microscopic study.

Microscopic Postmortem Examination—A preparation from the intact lung showed good-sized air spaces containing some cellular debris and occasional large mononuclear cells. Some of the air spaces were large. All the blood vessels appeared markedly distended with blood. The lining cells of the bronchi and bronchioles were well preserved. Another preparation from the same lung presented a similar structure. No cellular infiltration was noted.

A preparation from the left lung (figs 3 and 4) showed broad bands of vascular hyalinizing fibrous connective tissue and broad bands of a rather loose fibrous connective tissue. On both surfaces of these bands were mounted low cuboidal and cylindric cells. In places the surface was thrown into broad folds covered with cuboidal cells. Occasional bundles of smooth muscle and some lumens resembling acini of mucous or serous glands were noted beneath the epithelium-covered surfaces. In one place there was a strand of large mononuclear cells with golden yellow granular cytoplasm and nearby a few eosinophilic leukocytes. The capillaries



Fig 3 (case 1)—Photomicrograph showing multiple cystic spaces lined with low cuboidal and cylindric epithelium, thrown into folds which contain occasional bundles of smooth muscle and some lumens resembling acini of mucous or serous glands, $\times 40$

were distended with blood. Freshly extravasated blood was noted in some areas. Masses of granules staining blue and lavender were seen in the centers of some of the larger bands of connective tissue. Around some there were aggregations of cells and cell nuclei. In others the granular material lay free in the connective tissue, with no surrounding cellular reaction.

Staining revealed many areas of elastic tissue situated in the broad bands beneath the epithelial surfaces.

Comment—The right lung was apparently entirely replaced by many small and large cystic spaces with thin walls composed of cuboidal or cylindric nonciliated epithelium, loose fibrous tissue, occasional bundles of smooth muscle, mucous or serous glands and elastic fibers, indicating a bronchiogenic origin. There was no evidence of pneumothorax in either lung. The clinical course and the roentgenographic findings, together with the postmortem observations, clearly demonstrated that this was a case of multiple congenital pulmonary cysts, one or more of which were

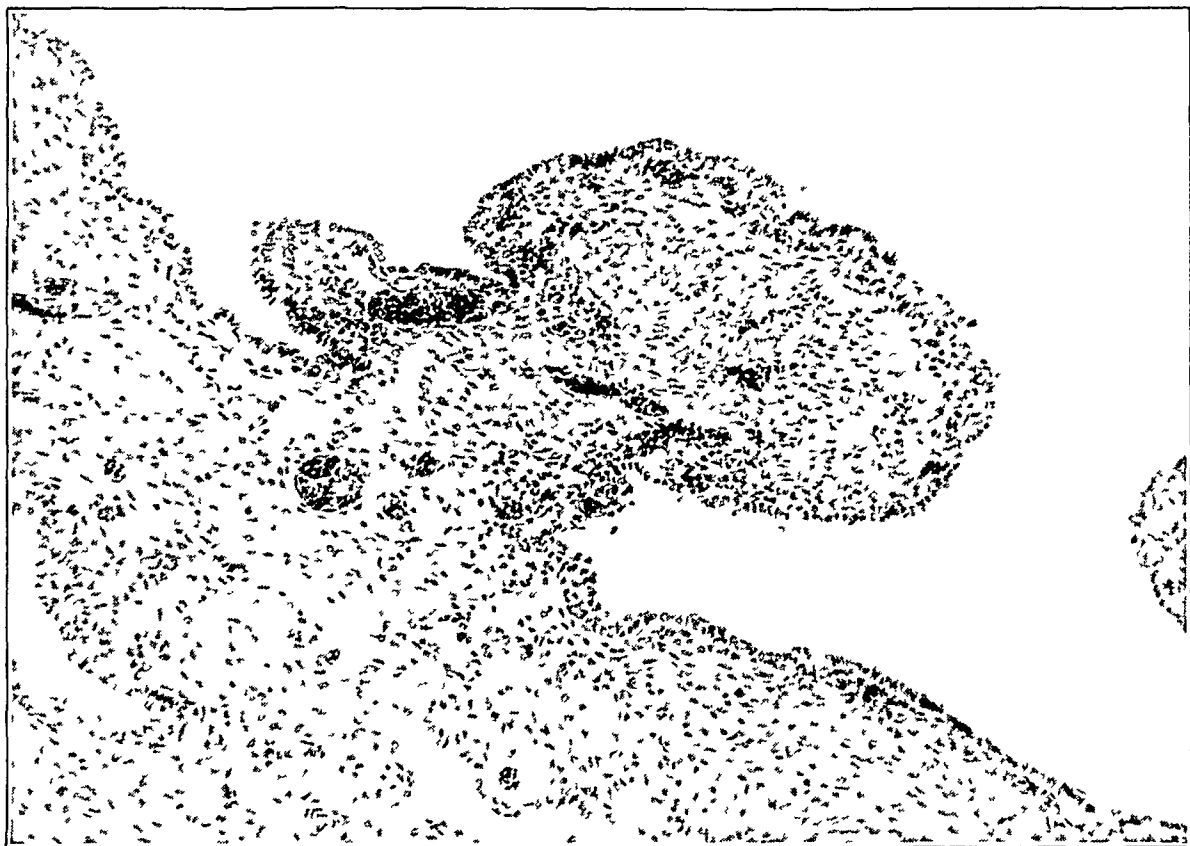


Fig 4 (case 1)—Photomicrograph showing details of a portion of the wall of one of the cystic formations, $\times 200$

of the expansile type, which accounted for the alarming symptoms of dyspnea and cyanosis resulting in sudden death.

CASE 2—N. F., a man aged 45 years, a shoemaker, came to the outpatient department with a history of pulmonary complaints for two years. The only symptom referable to the chest was a slight cough. Although his appetite was good, he believed that he had lost some weight. There were no sweats, elevation in temperature or weakness. Two years previously he was told that his lungs were affected. During this time he was at two institutions, where he was regarded as having tuberculosis, notwithstanding persistently negative results of examination of the sputum. This opinion was based on the roentgenographic examination, which showed what was interpreted as persistent pneumothorax at the base of each lung.

On physical examination the patient appeared well developed, well nourished and comfortable. There were diminished breath sounds at the base of both lungs, with sibilant and sonorous rales on both sides. The chest appeared emphysematous. Aside from the presence of atrophic rhinitis, the findings on examination were irrelevant.

Roentgenographic study (fig 5) revealed a large spherical area of transparency in the lower third of each lung extending to the diaphragm. A thin curvilinear shadow was observed superiorly, demarcating the air space from the normal lung. In the lateral view the cystic wall could be readily visualized. A dense opacity cast by compression of the lung obliterated the extreme costophrenic sulcus on each side. After the instillation of iodized oil into the bronchial tree (fig 6) the cystic spaces did not fill. The bronchial branches were displaced

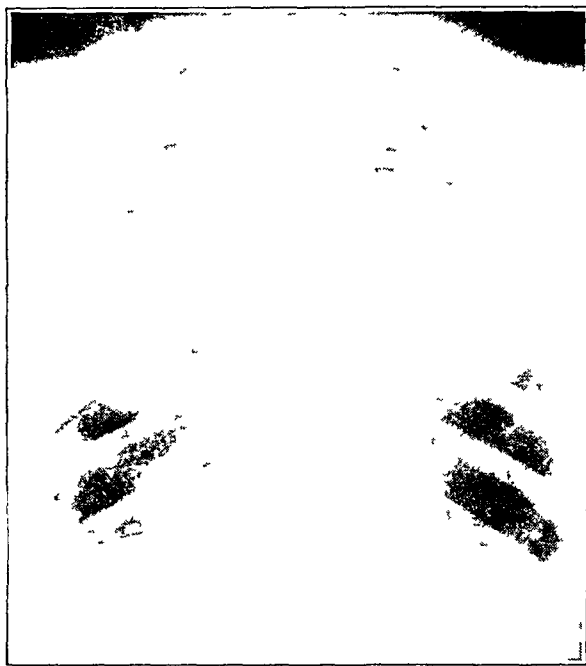


Fig 5 (case 2)—A large cystic space occupies the lower part of both lungs. The upper border of the cyst in each instance appears as a thin curvilinear shadow.

around the cyst and showed bronchiectatic changes. The roentgenographic impression was bilateral air cysts which probably communicated with a neighboring bronchus by a tortuous or imperfect channel, so that the iodized oil could not find its way into the cyst.

The Wassermann and Kahn tests showed a 4 plus reaction. A urologic survey revealed hypertrophy of the median lobe of the prostate. Neurologic and dermatologic examinations revealed no abnormality.

The patient was diligently observed for six years, during which time he received antisyphilitic treatment and roentgenologic studies were made. The physical signs and roentgenographic appearance of the lungs remained unchanged. At present there are no symptoms or complaints. The Wassermann and Kahn tests are negative. Yet the roentgenographic appearance of the lungs remains the same as at the first study made six years ago.

Comment—The presence of syphilis in no way alters the fact that this is a case of congenital pulmonary cystic disease. Syphilis has been considered by some observers as the underlying etiologic factor in this condition. However, negative results of serologic tests are most frequently encountered in patients with this pulmonary anomaly, and a complete autopsy usually reveals no stigmas of syphilitic infection. Hence the presence of syphilis is considered to be a coincidental rather than an etiologic finding.

The roentgenographic signs, unchanged for six years, lead to only one logical conclusion, namely, this is a case of congenital cystic disease.



Fig 6 (case 2)—*A*, the bronchographic medium failed to find its way through the tortuous, imperfect channel between the bronchus and the cystic cavity. The iodized oil visualizes the blunted bronchial branches, which end blindly. *B*, the oblique view shows the displacement of the bronchial tree by the cystic malformation, the delimiting border of which is more clearly depicted than in the anteroposterior view.

of the lung. Like many others of its kind, this case is a good illustration of minimal clinical symptoms with maximal roentgenographic findings, which are out of proportion to the patient's complaints and physical signs.

CASE 3—F. M., a woman 47 years old, complained of a dry chronic cough and shortness of breath for three years. She was the mother of four children, all living and well. Physical examination showed that she was obese and had a nonproductive hacking cough but was not in acute distress. The pharynx was moderately injected, and the voice was hoarse. Auscultation showed that the heart was normal. The lungs presented normal resonance, with slightly harsh

breath sounds in the right side of the chest. No râles were heard. The remainder of the examination gave unimportant results.

On roentgenographic examination (fig 7) a well circumscribed ovoid area of opacity was observed in the right side of the chest lying superior to the root. The shadow appeared homogeneous, with sharp borders. The mediastinal spaces showed no encroachment or displacement. The remaining lung bed was clear and the opposite pulmonic field likewise. The roentgenographic findings suggested an intrapulmonary tumefaction or a fluid cyst.

The Wassermann and Kahn tests were negative. Bronchoscopy showed the presence of extrinsic pressure on the trachea and the right main bronchus, the interior of which was normal.



Fig 7 (case 3) —An ovoid opacity is present in the right lung lying superior to the root and adjacent to the mediastinum. The shadow is intrapulmonary. No mediastinal encroachment is observed. The finding strongly suggests a solitary fluid cyst.

The patient was given several courses of high voltage roentgen treatments, with no effect on the symptoms or on the size and appearance of the opacity.

For over a year the roentgenographic appearance of the globular mass remained unchanged.

Comment —The roentgenologic diagnosis of a congenital fluid cyst is warranted from the appearance of the shadow, which shows no tendency to grow and which is entirely uninfluenced by intensive roentgenotherapy. Although repeated examinations were made during the course of a year, the roentgenographic findings remained unchanged.

CASE 4—J P, a man 29 years old, a baker, entered the outpatient department with the chief complaints of cough and pain in the chest for two years. Except for one sister, 26 years old, who had had pulmonary tuberculosis for three years, the family history was unimportant. At the age of 14 the patient had dry pleurisy, and at 15 he suffered from bronchitis. Two years before admission to the clinic he expectorated blood-tinged sputum over a period of a month. Since then he had been complaining of pains in the anterior portion of the chest and cough, occasionally expectorating white phlegm but no blood. There had been no afternoon fever and no night sweats. He felt strong and had gained about 40 pounds (18 Kg) in the past two years.

Physically the patient showed no abnormality aside from that in the chest—slight dulness in the apex of the right lung posteriorly and a few crepitant râles at the base of the left lung which disappeared with coughing.

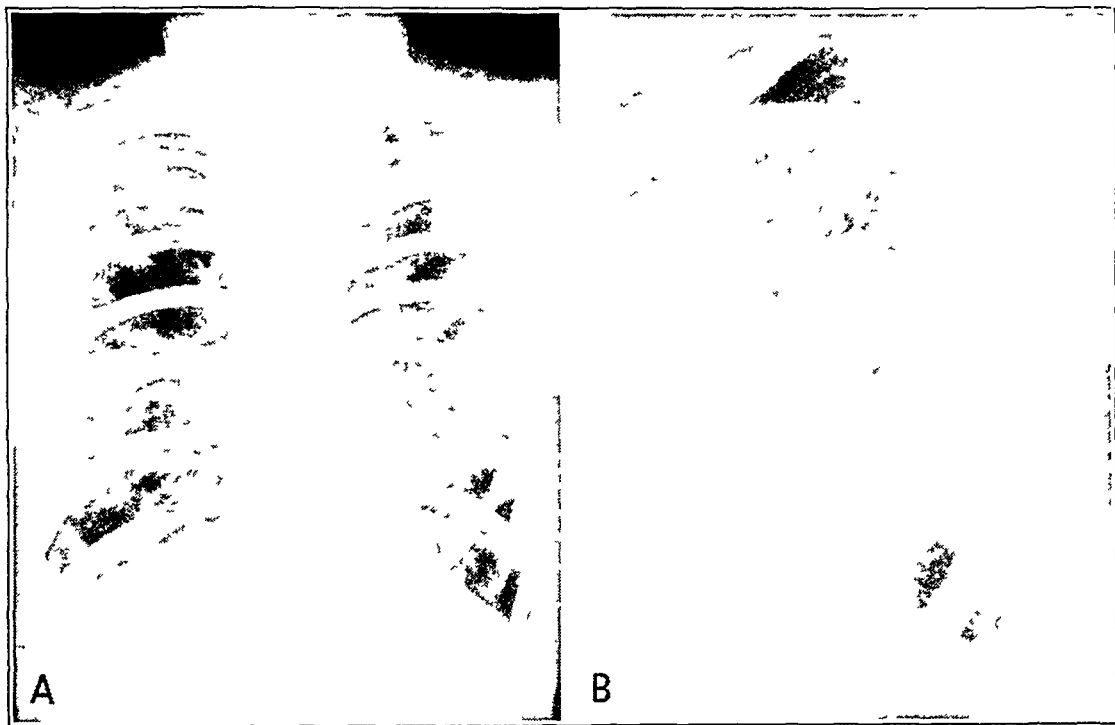


Fig 8 (case 4)—A, a small annular shadow is noted in the left pulmonary bed, slightly below and external to the root. The finding suggests the presence of a small solitary air cyst. B, the same portion magnified.

Roentgenographic study (fig 8) portrayed a small annular, or ring, shadow slightly below the midportion of the left thoracic field near the root. The shadow presented a well defined outer border and suggested the presence of a small solitary air cyst. A tuberculous cavity was not considered likely because of the location in the midthoracic field and the absence of perifocal infiltration. Both apices were clear, and no roentgenographic evidence of the concomitant infiltration of a tuberculous nature was found.

Passive bronchographic study revealed normal findings bilaterally. The iodized oil had apparently failed to enter the cystic cavity. No bronchiectasis or other abnormality was disclosed.

The patient was observed for more than a year, during which time no change in the roentgenographic findings was noted. Repeated examinations of the sputum revealed no tubercle bacilli.

Comment—A diagnosis of a tuberculous cavity can well be ruled out by the location of the lesion in the lower half of the pulmonary field, by the sharply defined, thin capsule, by the absence of other changes around the cyst and in the remaining portions of the lung, especially the apex, and by the constancy of the shadow, which remained unchanged in size and shape for a year. The patient's general good health, the uninterrupted gain in weight and the persistently negative results of examinations of the sputum strongly tend to exclude the presence of an ulcerative tuberculous lesion. The well defined membrane surrounding the small air pocket which persisted unchanged over a long period serves to exclude the possibility of an emphysematous bleb or bulla.

CASE 5¹²—N W, a woman 58 years old, presented a history of cough and loss of weight (70 pounds [32 Kg]) of one year's duration. Marked progressive weakness and dyspnea, with transient orthopnea, were additional symptoms. The cough was productive of small amounts of greenish sputum. There were no night sweats or afternoon fever. No previous history of disease of the respiratory tract was elicited.

When admitted to the hospital the patient showed a temperature of 98 F, a pulse rate of 88 and a respiratory rate of 21. The blood pressure was 132 systolic and 64 diastolic. Physical examination showed a poorly nourished, chronically ill woman who coughed frequently. The skin was loose, showing evident loss of weight. The eyes appeared sunken and the disks hazy. The teeth were decayed and the gums infected. The remaining examination revealed no abnormality except in the lungs. The expansion of the left side of the chest appeared greater than that of the right. No changes in the percussion note or breath sounds were noted. D'Espine's sign was not elicited. In the lower half of both pulmonary fields many mixed râles, persisting after coughing, were heard. The clinical impression was advanced bilateral tuberculosis. Repeated examination of the sputum failed to show the presence of the tubercle bacillus.

The roentgenographic examination (fig 9A) revealed considerable striping in the lower half of each pulmonary field, the apexes being relatively clear. There was a suggestion of a lattice-work appearance, with small annular shadows, often observed in bronchiectasis. The right diaphragmatic cusp presented an adhesion at the costophrenic angle. Bronchography (figs 9B and 10) revealed diffuse bilateral bronchiectasis of the saccular or cystic variety.

Comment—Without a previous history of severe respiratory infection to account for the present findings in the chest, in the absence of tubercle bacilli in the sputum at repeated examinations and with evidence of a diffuse involvement in both lungs, particularly in the lower half, the diagnostic impression of congenital cystic disease, often designated as congenital bronchiectasis and honeycomb lungs, is most plausible.

SUMMARY AND CONCLUSIONS

A total of 381 cases of congenital cystic disease of the lung, including 5 new cases here described, are analyzed, in groups according to the

12 Dr G H Koiransky gave me permission to report this case

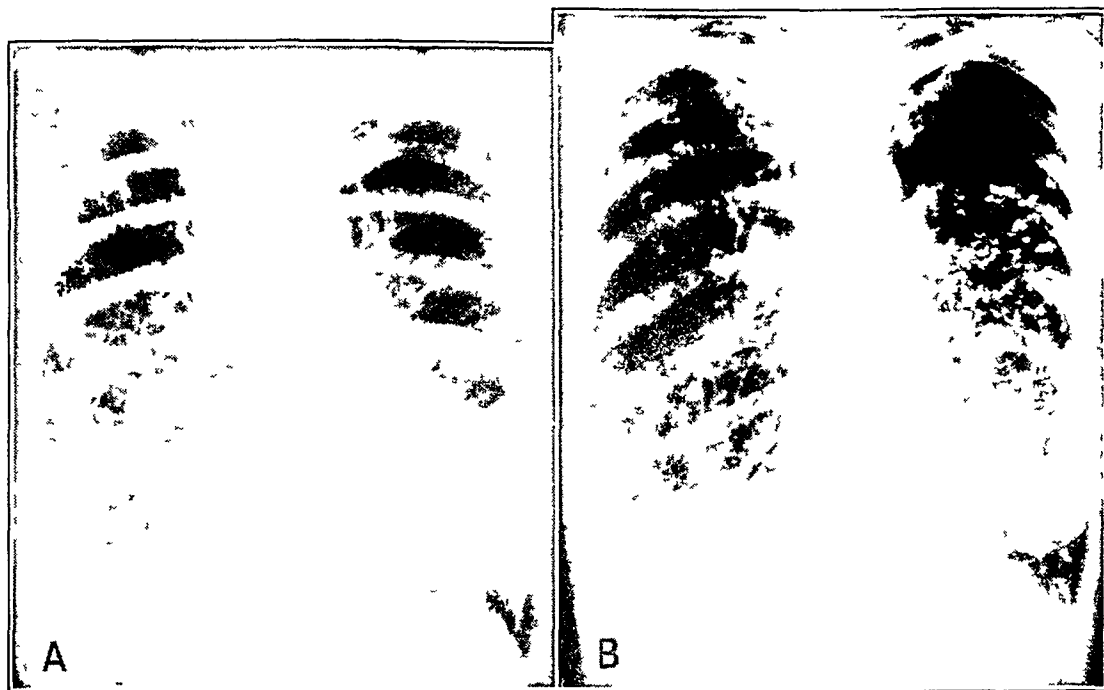


Fig 9 (case 5)—*A*, the lower half of each lung shows marked striping and many small annular shadows. A diaphragmatic adhesion is present in the right costophrenic sinus. The findings suggest bilateral bronchiectasis, probably of congenital origin. *B*, the polycystic cavities in the left lung are filled with the bronchographic medium. Note the presence of the small cystic areas in the lower portion of the upper lobe as well as in the lower lobe.

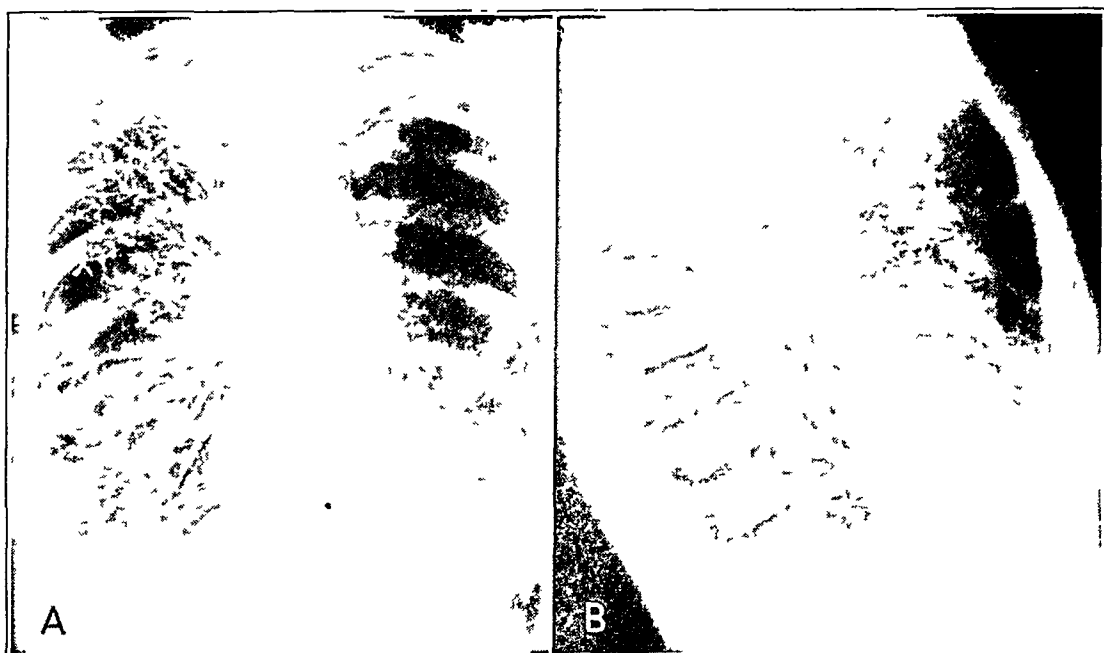


Fig 10 (case 5)—*A*, bronchographic study of the right lung shows innumerable small cavities throughout the entire pulmonary field. The widespread involvement indicates a polycystic lung. *B*, a lateral view of the chest shows the multiple small air cysts communicating with the bronchi, appearing partially filled with the iodized oil.

ages of the patients, in regard to sex, symptoms, type of cyst, cause of death and other characteristics. From this study the congenital pulmonary malformation is readily recognized by the history and the roentgenographic examination. In most cases the condition is diagnosed by roentgenograms alone. The main difficulty is to differentiate this congenital malformation from acquired cystic lesions, which can usually be accomplished by careful study and observation.

The following points are reiterated for emphasis

1 Congenital cystic disease of the lung is not a rare pathologic curiosity. Of the 381 cases reported in the literature, over 145 were recorded in the past two years.

2 With mild symptoms of respiratory disturbance dating from birth or early childhood, and in the absence of a history of severe infection of the respiratory tract, a congenital pulmonary malformation should be suspected.

3 The persistently unchanged roentgenographic findings usually indicate a congenital cystic lesion, whereas in acquired conditions follow-up roentgenograms show relatively frequent changes.

4 The lesion is usually attended with grave prognostic dangers in infants and young children who present the large cystic defect of the expansile type.

5 In older patients the malformation may not be incompatible with long life.

6 There are only 5 cases¹³ recorded in which the cystic space after emptying its contents collapsed and its wall absorbed and the patient recovered completely, with no visible evidence of the lesion in the roentgenograms.

7 Attacks of dyspnea and cyanosis, especially in infants and children, may be caused by a congenital cyst of the lung. Physicians must be cyst conscious in order to arrive at the correct diagnosis.

8 Pulmonary malformations must be considered among the causes for cyanosis of the new-born.

9 In children bronchiectasis limited to one lobe is usually of congenital origin.

10 Hemoptysis is a not uncommon symptom in congenital cystic disease of the lung. It was a prominent symptom in 52 cases.

13 Vollmer, H. Cystische Lungengebilde im Kindesalter, *Ztschr f Kinderh* **46** 810-817, 1928. Zarß, M. Zur Kenntnis der geschwulstformigen Luftansammlungen (Pneumatocelen) im Brustraum, *ibid* **54** 92-102, 1932. Croswell, C V, and King, J C. Congenital Air Cyst of the Lung, *J A M A* **101** 832-834 (Sept 9) 1933. Fleming, G B. Five Cases of Congenital Lung Cyst, *Arch Dis Childhood* **9** 201-212, 1934. Schenck, S G, and Stein, J L. Congenital Lung Cysts in Infants and Children, *Radiology* **24** 420-432, 1935.

11 An annular shadow or cystic space in the upper lobe may indicate a congenital anomaly and not necessarily a tuberculous vomica

12 The most important observation in the diagnosis of a pulmonary an cyst is the presence of the surrounding wall or delimiting membrane within the pulmonary parenchyma. A cystic wall should be looked for in the roentgenograms

13 A gross pathologic condition noted roentgenographically, with few or no symptoms or signs, often indicates a congenital malformation, such as a cystic lung

14 The treatment of choice is surgical, whenever feasible, provided the symptoms warrant such a dangerous procedure and the condition is limited to one lobe. The operation of choice is extirpation of the cyst, if possible, or lobectomy

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CAUSE OF DEATH IN TULAREMIA

LEE FOSHAY, M D

CINCINNATI

In the accumulating literature on clinical studies of tularemia there is expressed a growing belief that tularemic pulmonary complications are of ominous prognostic significance and that tularemic pneumonia is in itself the chief cause of death from this infection. Personal experience and a study of case records covering more than 750 cases of acute tularemia are not in agreement with this view. A survey of the morbidity and mortality data now available indicates that tularemic pneumonia cannot possibly be the chief cause of death.

FATALITY RATE

Up to the close of 1935 there had been reported to the United States Public Health Service 6,206 cases of tularemia, with 299 deaths, a fatality rate for the series of 4.8 per cent. Despite accurate methods for diagnosis, many nonfatal cases and an unknown number of deaths escape detection annually. The typhoidal clinical type is the one most frequently misdiagnosed. Also, as I shall show presently, this type carries a significantly higher mortality rate than the other clinical types. This leads me to believe that tularemic deaths are escaping recognition (and reporting) at a proportionally higher rate than 1/20 against nonfatal cases not reported on. I know at present of 2 such deaths, each from the typhoid type and recorded as due to "lobar pneumonia." This experience is doubtless not unique. Consequently I believe the true fatality rate is higher than the one recorded, and I should estimate this rate as not less than 6 per cent.

INCIDENCE OF TULAREMIC PNEUMONIA

A systematic roentgenologic study of the lesions of pulmonary tularemia is being carried out by Blackford¹ and his associates. Their last report² showed that in 33 of 35 cases selected at random there were

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1 Blackford, S. D. (a) Tularemia in Differential Diagnosis. A Review of Thirteen Cases, *Virginia M. Monthly* **58** 10 (April) 1931, (b) Pulmonary Lesions in Human Tularemia, *Ann. Int. Med.* **5** 1421 (May) 1932, (c) Pulmonary Manifestations in Human Tularemia, *J. A. M. A.* **104** 891 (March 16) 1935.

2 Archer, V. W., Blackford, S. D., and Wissler, J. E. Pulmonary Manifestations in Human Tularemia, *J. A. M. A.* **104** 895 (March 16) 1935.

abnormal bronchopulmonary findings. In 7 of the cases there was frank, clinically recognizable pneumonia, giving an incidence of pneumonia of 20 per cent. It is apparent that the great majority of intrathoracic tularemic lesions did not develop into gross pneumonic consolidations. Kavanaugh³ recorded the occurrence of pneumonia in 16 of 123 cases, an incidence of 12.7 per cent.

In the first 400 cases of tularemia for which I have precise data from the date of exposure to infection to the date of complete convalescence, there were 73 cases of clinically recognizable pneumonia, an incidence of 18.2 per cent. A summation of these three series shows 96 cases of frank pneumonia in 588 cases, an incidence of 17.2 per cent. Pneumonia of moderate degree is occasionally not detectable by physical signs alone. Also, it has been my experience and that of others to find that a number of cases of "pneumonia" or of "lobar pneumonia" were actually cases of tularemic pneumonia. In some cases cocci, especially pneumococci, were notably and repeatedly absent from specimens of sputum. Most of these cases occurred in the typhoid type of the disease which had been unrecognized. This type is more frequently associated with pneumonic lesions than are the other clinical types. Hence the true incidence of tularemic pneumonia is probably a little larger than the figures indicate. At present I think a fair estimate of the incidence of pneumonia would be not less than 18 per cent.

There is, then, a fatality rate of about 6 per cent and an incidence of pneumonia of about 18 per cent. Obviously the majority of cases of pneumonia are not represented by fatalities. Even if it could be assumed that every tularemic fatality was associated with pneumonia, it is apparent that in two thirds of the cases pneumonia could not possibly have terminated fatally. Furthermore, the assumption that fatalities are always associated with pneumonic lesions is not supported by clinical and postmortem experience. As will be shown later, a large proportion of tularemic deaths occur without any clinical or necropsy evidence of such lesions. Thus the morbidity and mortality data will not support the belief that pneumonic lesions are the chief cause of tularemic deaths. These data suggest that some other lethal factor is responsible for the majority of deaths and that this other factor operates independently of the presence or absence of pneumonia.

EVIDENCE FROM A STUDY OF EIGHTY-FIVE FATALITIES

The left half of table 1 shows the distribution of my 400 cases according to the four clinical types defined by Francis⁴. It shows also

³ Kavanaugh, C. N. Tularemia. A Consideration of One Hundred and Twenty-Three Cases with Observations at Autopsy in One, *Arch Int Med* **55** 61 (Jan) 1935.

⁴ Francis, E. Tularemia, *Atlantic M J* **30** 337 (March) 1927.

the frequency of pneumonia in each type and the incidence per hundred cases. It will be noted that the ulceroglandular type, the most frequent clinical form, accounts for most of the cases of pneumonia, although the incidence of pneumonia is only 15.4 per cent. It is notable that the incidence of pneumonia is significantly higher in the typhoid type. Although in only 8 per cent of cases was this clinical form presented, in 53 per cent there was pneumonia, and the type accounted for almost one fourth (23.3 per cent) of the total number of cases of pneumonia.

The right half of table 1 shows the corresponding distributions and rates in 85 fatal cases of tularemia. Data for these fatal cases were compiled from published reports, from my own cases and cases studied in consultation and from records supplied by physicians who had observed hitherto unreported deaths. A summary of these data is given

TABLE 1—*The Incidence of the Four Clinical Types of Acute Tularemia and the Frequency of Pneumonia in Four Hundred Unselected Cases and in Eighty-Five Fatal Cases*

Type of Tularemia	400 Unselected Acute Cases				85 Fatal Cases			
	No of Cases	Per centage	No of Cases of Pneu monia	Per centage	No of Cases	Per centage	No of Cases of Pneu monia	Per centage
Ulceroglandular	351	87.8	54	15.4	50	58.8	25	50.0
Glandular	10	2.5	1	10.0	1	1.2	0	0.0
Oculoglandular	7	1.8	1	14.3	5	5.9	2	40.0
Typhoidal	32	8.0	17	53.1	29	34.1	21	72.4
Totals	400		73	18.2	85		48	56.5

in tables 2 and 3. Necropsies were performed in 43 cases, and pneumonia was present in 28 cases and absent in 15. In the 42 cases in which pneumonia was diagnosed by physical signs alone, it was present in 19 and absent in 18. No certain information is available in 5 cases. Here it is probable that the lack of specific record means that no pneumonia was discovered on gross examination. However, excluding these doubtful cases, it may be noted that the failure to find pneumonia by physical signs alone (in 43 per cent) is in good agreement with the failure to find it in the series in which necropsy was performed (35 per cent).

Table 1 shows that the greatest number of deaths occurred from the ulceroglandular type of tularemia, the type with the highest incidence, but that only half the total number of deaths were associated with pneumonia. Indeed, with a total incidence of pneumonia of 56.5 per cent, it is apparent that only slightly more than half of all the fatalities were associated with pneumonic lesions. Pneumonia appeared three times as frequently in the fatality as in the general series. The typhoid type

of disease appeared more than four times as frequently in the fatal cases than it did in the general group. One third of all deaths were caused by the typhoid type, and 72 per cent of deaths from this type were associated with pneumonia.

On the basis of these data it is clear that pneumonia appeared in only 56 of 85 unselected fatal cases, that pneumonia appeared in approximately the same ratio in cases in which necropsy was performed as in an equal number of cases in which it was not performed, that pneumonia appeared much more frequently in the typhoid type than in the three other clinical types, that the mortality rate of the typhoid type is significantly higher than the rates of the other types, but that this increased mortality cannot be entirely ascribed to the presence of pneumonic lesions, since in almost one third of the fatal cases of this type (29 per cent) pneumonia was not noted.

Patients with the ulceroglandular, glandular and oculoglandular types show involvement of the dermal, subdermal and regional lymphatic channels and nodes. Although Francis⁴ has demonstrated that transient bacteremia occurs in the early phases of infection, the fixed lymphatic tissues seem to bear the brunt of the initial invasion in these three types. The typhoid type differs notably in this respect. There is either minor cutaneous or regional lymphatic involvement or, most commonly, none at all. In this type the infection is generalized from the onset, and multiple focal lesions are prone to develop in deep organs and tissues, especially in the lungs, with earlier impairment of important structures. The reasons for this difference are obscure, but the differential mortality rates suggest that the lack of involvement of superficial tissue in the typhoidal type might be an immunologic handicap. It may be that extensive dermal and subdermal invasion is actually of benefit to the patient and that these superficial localizations result in a stimulation of immune responses which rapidly raise the general level of tissue and humoral defenses.

Man is highly susceptible to tularemic infection, but once the disease has been acquired the great majority of patients exhibit a marked degree of natural resistance. This is borne out by the low mortality, by the histologic evidence of subacuteness and chronicity of the cellular reactions and by the infrequent establishment of chronic progressive infection. The initial bacteremia, apparently analogous to the early transient bacteremia that occurs in typhoid fever, seldom persists as septicemia, although it almost certainly is the source of a moderate number of scattered solitary foci of necrosis in various organs which, if death should supervene, are recognizable as isolated large foci 0.5 to 1.5 cm in diameter, most frequently in the liver, spleen and lungs.

TABLE 2—Synopsis of the Clinical and Postmortem Data in Forty-Three Cases

Number of Case	Patient	Age	Sex	Type	Day of Disease at Death	Clinical Data				Necropsy Data				Complications	Authors
						Pneumonia	Involvement of Central Nervous System	Enlargement of Liver and Spleen	Involvement of Gastro Intestinal Tract	Pneumonia	Involvement of Central Nervous System	Nodular Pulmonary Foci	Miliary Sepsis		
1	"Jones"	62	M	U	18	0	0	++	0	0	0	++	++	++	Hartman, Beaver and Green ¹⁷
2	Mrs C S	67	F	U	18	0	+	0	0	0	0	++	++	++	Verbruycke ⁸
3	Mrs M C	35	F	G	5th mo	+	0	0	0	0	0	++	++	++	Francis and Callender ⁹
9	?	40	M	U	18	+	0	0	0	+	0a	0	+	+	Massee ¹⁵
14	T M P	45	M	U	18	0	+	0	0	0a	+	0	+	+	Halzip and O'Neill ²⁸
15	A R C	32	F	U	8	0	+	0	+	0b	+	0	+	+	Palmer and Hansmann ¹³
16	B I S	37	F	U	22	+	+	+	+	+	+	+	+	+	Foulger, Glazer and Foshay ¹⁰
17	T P	32	M	T	30	+	+	+	+	+	+	+	+	+	Gudger ²⁰
20	T W	23	M	U	5	0	+	0	+	0	0	+	+	+	Simpson ¹²
23	V B	53	M	U	15	+	+	0	0	+	+	+	+	+	Bardon and Berdez ¹⁰
25	I G F	65	M	U	14	+	+	0	0	+	+	+	+	+	Bunker and Smith ¹⁴
26	A T R	29	M	U	14	0	+	+	+	0	0	0	+	+	Goodpasture and House ¹¹
27	J C P	43	M	T	16	0	+	+	+	0	0	0	+	+	Asbury, W D J Indiana M A 19 ⁴⁰⁴ , 1926
30	R S	52	M	U	26	+	0	0?	0	Partial	Partial		+	+	Francis, E Harvey Lectures, 1927 1928, Baltimore, Williams & Wilkins Company, 1929
32	L K	24	M	U	29	0	0	+	+	0	0	0	+	+	Bryant and Hirsch ²⁶
38	W S	48	M	U	16	0	+	+	0	+	+	+	+	+	Hartman ²⁷
39	?	50	M	U	36	0	+	0	0	0	0	+	+	+	

TABLE 3—Synopsis of Clinical Data in Forty-two Fatal Cases of Tularemia in Which Necropsy Was Not Performed

Number of Case	Patient	Age	Sex	Type	Day of Disease at Death	Pneumonia	Involvement of Central Nervous System	Enlargement of Liver and Spleen	Involvement of Gastro Intestinal Tract	Complications	Authors
1	P J L	37	M	O	8	0	0	0	0		Freese, H L, Lake, G C, and Francis, E Pub Health Rep 41 369, 1926
5	O L	7	F	O	8	0	0	0	0		Freese, H L, Lake, G C, and Francis, E
6	L W	2	M	O	6	0	0	0	0		Freese, H L, Lake, G C, and Francis, E
7	B S	37	M	U	36	0	0	+	+	Nephritis	Moloney, F J†
8	F S	6	M	U	47	0	0	+	+	Hypertension, nephro sclerosis	Eberly, K O†
10	I W	62	F	U	23	+	0	+	+		Carothers, C J†
11	R B	36	M	T	9	+	+	+	+		Foshay
12	T B	53	M	U	12	+	+	+	+		Huether, W W†
13	E B	60	F	U	16	+	+	+	+		Foshay
18	C H	67	M	U	17	+	+	+	+		
19	S D	55	F	T	4th mo	+	+	+	+		
21	G D B	48	M	U	9	0	+	+	+		Kavanaugh, C N Kentucky M J 25 352 1927
22	J L	51	M	U	12	0	?	?	+		Francis, E De Lamar Lectures, 1926 1927, Baltimore, Williams & Wilkins Company, 1928
24	Mrs J H	53	F	U	14	0	+	?	+		Francis, E
28	W N	53	M	U	16	0	+	?	+		Rutledge, L H J A M A 88 788, 1927
29	J B S	53	M	U	23	+	+	?	0		Francis, E
31	L N	40	M	U	28	0	0	0	0	Heart disease	Francis, E
33	Fuhrer's	41	F	U	31	0	0	0	0	Heart disease	Francis, E
34	T J R	31	M	U	34	0	0	0	0		Francis, E
35	B W B	66	M	U	41	+	0	?	0		Francis, E
36	C H W	31	M	U	8th wk	+	+	?	0		Francis, E
37	L B	42	M	U	3d mo	+	+	?	0		Francis, E
41	R W	32	M	U	15	?	+	?	0		Pearse, R A Northwest Med J 81, 1911
43	R W	60	M	U	52	+	+	+	+		Boyer, S, Jr†
46	Baby	1	M	U	4	+	+	+	+		Crawford, M J A M A 99 1497, 1932
47	J O	2	F	T	6	0	+	?	+		Crawford, M
48	C O	10	M	T	28	+	+	?	+		Crawford, M
52	Bl (34)	42	F	T	16	+	?	?	+		Crawford, M
54	Ch R	61	M	T	15	+	0	?	+		Blackford ab
57	L M	58	M	T	48	+	0	+	+		Carlson, B†
59	W O	23	M	T	14	+	0	+	+		Stout, R B†
60	W O	50	F	U	26	+	+	+	+		Kavanaugh
61	S D	36	F	U	3½ mo	+	+	+	+		Kavanaugh
62	S D	65	F	T	10	+	+	+	+		Kavanaugh
63	J M	34	F	T	24	+	+	+	+		Foshay
68	E H	73	F	T	24	+	+	+	+		Foshay
70	O B	23	F	T	12	+	+	+	+		Cook, F E†
75	G S	31	M	T	67	+	?	?	+		Amoss and Sprunt 20
78	P McE	23	M	T	7	0	0	+	+		Hunt, G O†
80	M R	65	F	U	18	0	0	+	+		Huesman, A†
81	?	28	M	U	18	+	0	+	+		Preston 21
83	G W	35	M	U	14	+	+	+	+		Perret, J M†

Other common sites are lymph nodes and, possibly, bone marrow.⁵ These isolated foci of necrosis may serve as points of origin of a second, later bacteremia. Also in the lung they may initiate either florid or abortive pneumonia.

Chart 1 shows the day of disease on which death occurred in the 74 cases in which the disease terminated fatally during the first seven weeks of illness. Most deaths occurred on the sixteenth day of disease (mode, 16.4 day).

To the left of the vertical line in chart 1 are recorded a small group of deaths that occurred from the fourth to the tenth day of disease. These 14 deaths represent cases 4 to 6, 11, 15, 20, 21, 44 to 47, 63, 80 and 84 recorded in the tables. Five of these (cases 15, 20, 44, 45 and 84) came to necropsy. In only 2 (cases 45 and 84) was pneumonia present, in case 45 a single small area being noted. The pulmonary changes in case 15, described by Palmer and Hansmann as "inconsider-

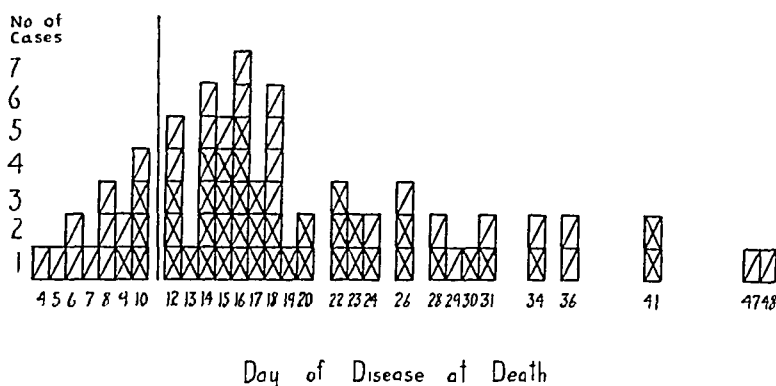


Chart 1—Day of disease at time of death in 71 cases in which death occurred during the first seven weeks of illness. In charts 1 and 2 the crossed diagonals indicate pneumonia present at death, and the single diagonals, no pneumonia.

able," were so minor that they were regarded as insignificant as a cause of death. In the remaining 9 rapidly fatal cases, pneumonia of lobar distribution was the diagnosis in only 2 cases (cases 11 and 63). There is lack of specific record in case 21. In the other 6 cases there was no clinically recognizable pneumonia. In only 4 of the 13 cases in which there is specific record was pneumonia present. The chief necropsy observations were of myriads of submiliary to miliary focal necroses, especially prominent in the enlarged liver and spleen but also present in the lungs (in 4 cases) and to a much less extent in the serosae, kidneys, adrenal glands and other tissues. Those familiar with the postmortem appearance of small laboratory animals will agree that this brief description applies satisfactorily to the gross anatomic changes of

⁵ Francis, E. Bone Marrow in Tularemia, *Pub Health Rep* **48** 1127 (Sept 15) 1933. Yamaguchi, M. Experimentelle Studien über die Hasenkrankheit (Yato-byo, Ohara), *Tr Jap Path Soc* **21** 499, 1931.

rodent tularemia Most rodents have no natural resistance to tularemia, and in them the disease is almost invariably a fatal septicemia of brief duration, usually of from four to ten days If the resistance is raised artificially before the animal is infected the survival period can be greatly prolonged, and the tissues then show subacute and chronic lesions comparable to those usually noted in man Downs⁶ found that rabbits partially protected by vaccination with formaldehyde-treated suspensions reacted to infection by the production of subacute lesions By previous serial use of chemically modified vaccines and antitularemia serums I have seen chronic fibrous lesions develop in infected guinea-pigs from strains of high virulence It seems obvious to me that this group of 14 patients (chart 1) had no natural resistance to tularemic infection and that they reacted to invasion just as normal rodents do The clinical course in each instance was that of acute septicemia Six patients had symptoms referable to the intestinal tract, 5 had prominent symptoms referable to the central nervous system One child died in convulsions Five cases occurred in children less than 10 years of age The cause of death seems certainly to be the tularemic septicemia

To the right of the vertical line in chart 1 are recorded deaths that occurred from the twelfth to the forty-eighth day of disease In these cases there was evidence of some degree of resistance to the infection A review of the clinical course in each case makes it seem improbable that death was due to sepsis resulting from the primary bacteremia, although in 3 cases there was possibility of extension of the primary bacteremia into the septicemia that preceded and apparently caused death In the large majority of cases there was a period of variable length, usually a week or more, during which the fever was low to moderate and when symptoms and signs of intoxication, and of the extent of the disease, were no greater than those in the majority of cases of nonfatal infection Nevertheless the postmortem observations when necropsy was performed and the antemortem clinical findings when necropsy was not performed indicate that death was preceded by, and probably caused by, septicemia Examination of the condensed clinical and necropsy data in tables 2 and 3 will show that this is true for the great majority of fatalities It will be noted that the exceptions fall chiefly into two classes cases in which precise diagnostic information was unobtainable and cases in which the patient was already the victim of some other serious morbid state at the time tularemia was acquired In the latter group cardiac disease is the most frequent Nine deaths in this series were complicated by previous or coexisting cardiac disease

6 Downs, C M Immunologic Studies on Tularemia in Rabbits, *J Infect Dis* 51 315 (Sept-Oct) 1932

Four patients had previous coronary disease, and 3 deaths were due to coronary occlusion that occurred during convalescence and after the fever had subsided. In only 1 of these 4 patients had anginal attacks occurred prior to the onset of tularemia. Two patients who died had complicating streptococcic subacute bacterial endocarditis demonstrated at necropsy. Three other deaths were due to heart failure which occurred after the severe febrile phase of tularemia had been safely passed. In 2 cases the exact nature of the preexisting cardiac disease is not known. The third case was that of a patient who showed generalized arteriolar sclerosis with arteriolar nephrosclerosis, hypertension and cardiac hypertrophy and who died, afebrile, almost seven weeks after the onset of tularemia. These observations, together with others recorded elsewhere,⁷ indicate that tularemia is especially dangerous to the life of the patient with preexisting cardiac disease and more especially with coronary disease. Records of additional cases of survival, with continuing attacks of angina and electrocardiographic signs of coronary disease, all with the clinical onset subsequent to tularemic infection, further emphasize this danger.

The chief clinical signs of septicemia are rapid and progressive enlargement of the liver and spleen, sometimes with steadily increasing jaundice, a temperature curve that is either continuously at a high level or of the widely swinging, daily-remittent type with high peaks, the pulmonary and constitutional signs (hyperpnea and warm cyanosis) which are usually associated with pulmonary miliary tuberculosis, signs of meningeal or cerebral involvement, diarrhea, tympanites, multiple areas of progressing bronchopneumonic lesions, usually becoming confluent, urinary findings of acute hemorrhagic nephritis or of intense acute nephrosis, and progressive involvement of the pleurae, pericardium and peritoneum.

Review of the cases reported in which necropsy was performed shows that the most constant lesions are foci of necrosis, of miliary to submiliary size, diffusely scattered throughout the liver and spleen and to a less extent in the serosae, kidneys and adrenal glands. They often occur in the lungs, with and without concomitant pneumonia. This has also been the situation in 7 of the 9 necropsies I have attended. Complicating cardiac disease was present in each of the other 2. In the cases reported by Veibrycke,⁸ Francis and Callender,⁹ Bardon and

7 Foshay, L., and Mayer, O. B. Viability of *Bacterium Tularensis* in Human Tissues, *J. A. M. A.* **106** 2141 (June 20) 1936.

8 Veibrycke, J. R. Tularemia, with Report of a Fatal Case Simulating Cholangitis, with Postmortem Report, *J. A. M. A.* **82** 1577 (May 17) 1924.

9 Francis, E., and Callender, G. R. Tularemia. Microscopic Changes of the Lesions in Man, *Arch. Path.* **3** 577 (April) 1927.

Berdez,¹⁰ Goodpasture and House,¹¹ Simpson,¹² Palmer and Hansmann,¹³ Bunker and Smith,¹⁴ Massee,¹⁵ Permar and MacLachlan,¹⁶ Hartman, Beaver and Green,¹⁷ Kavanaugh,³ Blackford,¹⁸ Foulger, Glazer and Foshay,¹⁹ Amoss and Sprunt,²⁰ Bernstein,²¹ Preston²² Gundry and Warner,²³ Beck and Merkel²⁴ and Pessin,²⁵ there was ample evidence to show that septicemia preceded death. In addition, in the cases of Bryant and Hirsch²⁶ and Hartman²⁷ necrotic foci showed in the meninges and cerebral substance, respectively and in the case of Haizlip

10 Bardon, R, and Berdez, G Tularemia Report of Fatal Case with Post-mortem Observations, *J A M A* **90** 1369 (April 28) 1928

11 Goodpasture, E W, and House, S J Pathologic Anatomy of Tularemia in Man, *Am J Path* **4** 213 (May) 1928

12 Simpson, W M Tularemia Study of a Rapidly Fatal Case, *Arch Path* **6** 553 (Oct) 1928

13 Palmer, H D, and Hansmann, G H Tularemia Report of Fulminating Case with Necropsy, *J A M A* **91** 236 (July 28) 1928

14 Bunker, C W O, and Smith, E E Tularemia Report of Four Cases, One Fatal, with Autopsy Report, *U S Nav M Bull* **26** 901 (Oct) 1928

15 Massee, J C Tularemia in Georgia Report of a Fatal Case, *J M A Georgia* **20** 66 (Feb) 1931

16 Permar, H H, and MacLachlan, W W G Tularemic Pneumonia, *Ann Int Med* **5** 687 (Dec) 1931

17 Hartman, H R, Beaver, D C, and Green, R G The Occurrence of Tularemia in Minnesota in 1921 Report of Two Cases, One Fatal, with Necropsy Report, *Minnesota Med* **16** 559 (Sept) 1933

18 Blackford^{1b} Archer, Blackford and Wissler²

19 Foulger, M, Glazer, A M, and Foshay, L Tularemia Report of Case with Postmortem Observations and Note on Staining of Bacterium Tularensis in Tissue Sections, *J A M A* **98** 951 (March 19) 1932

20 Amoss, H L, and Sprunt, D H Tularemia Review of Literature of Cases Contracted by Ingestion of Rabbit and the Report of Additional Cases with a Necropsy, *J A M A* **106** 1078 (March 28) 1936

21 Bernstein, A Tularemia Report of Three Fatal Cases with Autopsies, *Arch Int Med* **56** 1117 (Dec) 1935

22 Preston, B S Tularemia Report of Fatal Case, *West Virginia M J* **27** 28 (Jan) 1931

23 Gundry, L P, and Warner, C G Fatal Tularemia Review of Autopsied Cases with Report of a Fatal Case, *Ann Int Med* **7** 837 (Jan) 1934

24 Beck, H G, and Merkel, W C Tularemia Fatal Case of the Typhoid Form Caused by Ingestion of Rabbit, Autopsy Report, *South M J* **28** 422 (May) 1935

25 Pessin, S B Tularemic Pneumonia, Pericarditis and Ulcerative Stomatitis, *Arch Int Med* **57** 1125 (June) 1936

26 Bryant, A R, and Hirsch, E F Tularemic Leptomeningitis Report of Case, *Arch Path* **12** 917 (Dec) 1931

27 Hartman, F W Tularemic Encephalitis Pathology of Acute Tularemia with Brain Involvement and Coexisting Tuberculosis *Am J Path* **8** 57 (Jan) 1932

and O'Neil²⁸ a pure culture of *Bacterium tularensis* was obtained from the spinal fluid by inoculation into laboratory animals. In Blackford's case 5^{1b} there was not much evidence for general septicemia, as only two microscopic foci were seen in the liver, and none were noted in the spleen. However, in addition to bronchopneumonia there were multiple foci of miliary size in the unconsolidated areas of the lungs. The appearance was similar to that of pulmonary miliary tuberculosis in which little or no bacterial dispersion occurred in the systemic circulation. In Gudger's²⁹ case likewise there were no foci in the liver or spleen, but there were some in the lung in addition to the pneumonia. There were clinical signs indicating involvement of the central nervous system during life, and cultures of *Bact. tularensis* were obtained from the heart blood and from the spleen and again from the spleen by rabbit inoculation after death. This death appeared to be due to pulmonary miliary tularemic sepsis and pneumonia, with generalized terminal septicemia, in the strict sense of the term. The case of Fetterman and Lerner³⁰ is similar to that of Gudger, though it is not clear whether miliary foci were present in the lung in addition to the pneumonia and the large areas of caseation necrosis. Only foci of microscopic size were noted in the spleen, apparently none, in the liver. In Lewy's³¹ case death occurred on the twentieth day of disease from pulmonary embolism secondary to thrombophlebitis of the inferior cava. Here also there were no signs of systemic sepsis, but miliary foci were in the lungs in addition to the pneumonia. In 13 of the 15 cases studied post mortem and reviewed by Gundry and Warner,²³ the necrotic foci were of miliary size or larger. This was also true in the necropsies attended by me. As the size of the foci is an indication of their ante-mortem duration, it is probable that the onset of the septicemia in these cases occurred at least four days ante mortem. In only 9 of the 15 cases was there pneumonia of sufficient extent to warrant its consideration as a cause of death. As multiple necrotic foci were observed in the liver in each case, in the spleen in every case but 1 and in the lungs in 6 cases, I believe the pathologic evidence for cause of death is much greater for death from tularemic sepsis than for death from pneumonia. The bronchopulmonary lesions are of hematogenous origin. The majority of such lesions that arise from the primary bacteremia

28 Hazlip, J. O., and O'Neil, A. E. A Case of Meningitis Due to *Bacterium Tularensis*, *J. A. M. A.* **97** 704 (Sept. 5) 1931.

29 Gudger, J. R. Tularemic Pneumonia. Report of a Case, *J. A. M. A.* **101** 1148 (Oct. 7) 1933.

30 Fetterman, G. H., and Lerner, H. Fatal Case of Tularemic Pneumonia with Associated Ileitis. Clinical and Pathologic Report, *J. Lab. & Clin. Med.* **21** 1157 (Aug.) 1936.

31 Lewy, R. B. Pulmonary Tularemia, *Illinois M. J.* **70** 192 (Aug.) 1936.

fail to develop into pneumonic areas of any significant size. The lesser number that do become areas of frank pneumonia do not, in the absence of septicemia, become associated with fatalities but eventually are classified with the larger group (about 70 per cent) of lesions in nonfatal cases of tularemia with pneumonia. Pneumonia that arises either simultaneously with or after the onset of septicemia is certain to be recorded among fatalities. The greater frequency of pneumonia in the typhoidal type is correlated with the greater frequency of septicemia in this type. Even so, 29 per cent of deaths from this type occur from septicemia without the concomitant production of pneumonia.

In the first group of rapidly fatal cases the primary bacteremia was maintained as a septicemia which caused death. In this second group, comprising the majority of fatal cases, it is probable that the initial bacteremia did not persist, except possibly in a few cases. It is apparent then that septicemia usually arises from a second invasion of the blood stream and the origin of this second bacteremia and its causes are of great importance. Goodpasture and House³¹ suggested that one mode of origin was similar to that which commonly precedes the onset of miliary tuberculosis, the erosion of a vascular wall by an encroaching necrotic focus and the discharge of its infectious contents into the circulation. Foci established by the primary bacteremia in the lungs, liver, spleen and bone marrow might well serve as points of dispersion. Also, foci established in lymph nodes by direct lymphatic extension from a primary lesion may serve similarly. Landay³² reported a case which indicated the possibility of direct extension of bacteria through the lymphatic drainage into the venous circulation. His patient acquired a primary lesion on the right leg, just above the knee. The superficial inguinal nodes became enlarged four days later, and one progressed rapidly to suppuration and spontaneous rupture. The deep inguinal nodes also became enlarged, and soon thereafter a mass the size of a large orange appeared rising out of the right iliac fossa. This indicated rapid bacterial penetration through the superficial and deep inguinal nodes into the iliac nodes. Many patients show extension of infection from the superficial nodes of the arm to the superficial and then to the deep nodes of the axilla and thence to the subclavian or infraclavicular nodes. As such extensions are not infrequent, the likelihood of further penetration to the thoracic duct or right lymphatic duct must be rather great. Direct lymphatic extension deserves consideration as a possible mode of origin of septicemia.

This study of fatal infection indicates that the duration of tularemic sepsis is usually short, seldom exceeding ten days. The average duration of life after the onset of septicemia is about a week. It is unknown whether the defense mechanism breaks down prior to the onset of sepsis.

32 Landay, L. H. Personal communication to the author.

or subsequent to it, but observations in 450 cases after specific serum therapy lead to the belief that resistance is not lost until after sepsis has occurred. In no case in which septiceimia was not present at the time serum was given did it develop. The deaths that did occur in these cases were almost never due to tularemia alone. In all instances the condition was complicated by some other disease, usually coronary heart disease, and almost all of these diagnoses were verified by necropsy. Serum therapy seems definitely to prevent the occurrence of tularemic septiceimia. Furthermore, 2 patients with classic signs of general sepsis, 1 with readily palpable liver and spleen and steadily increasing icterus and the other with additional frank signs of focal cerebral lesions, have made permanent recoveries as a result of serum therapy. It is probable that the resistance of tularemic patients at this phase is similar to that of tuberculous patients just prior to the onset of miliary tuberculosis.

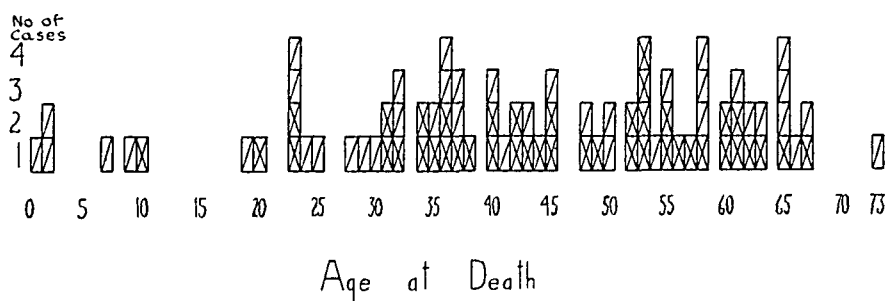


Chart 2—Ages at death according to single years

An important therapeutic inference arises from these studies. Most of the deaths recorded to the right of the vertical line in chart 2 were caused by tularemic sepsis occurring as a result of the second invasion of the blood stream. As the administration of antitularemia serum prevents the initiation of this septiceimia, the inference is clear that had serum therapy been given early in the disease in all cases in this group, survival would have been noted in the great majority. Strong support for this reasoning is contained in records I have of cases in which treatment with serum was given on or before the twelfth day of disease. In this group were 105 cases in which no septiceimia, coronary heart disease or other serious complication was noted. No deaths occurred.

A disturbing clinical feature of tularemic sepsis is that no forewarning of its occurrence is evident. It is known in general that in 1 case in every 17 sepsis is destined to develop, but at present I know of no sign or symptom that foretells its onset. I am reluctant to advise early serum therapy as a routine for a disease with such a low mortality, but at present I can see no other means of preventing these deaths. One of my fatal cases is noteworthy, as it illustrates the most treacher-

ous potentiality of tularemia, the abrupt and unpredictable onset of fatal septicemia in a patient whose symptoms up to that moment had been unusually mild

C H, aged 67, and his daughter-in-law, E H, aged 32, were infected simultaneously with tularemia when cleaning wild rabbits. Each had an incubation period of three days, followed by the typical onset and course of the ulceroglandular type of tularemia, with positive agglutinin titers of 1:160 and 1:80, respectively, on the tenth day of disease. Antitularia serum, then in its first year of clinical trial, was offered to the attending physician on the eighth and tenth days of disease but was declined on the apparently reasonable grounds that in both cases the involvement was of mild severity and the patient was doing well. On the eleventh day of disease the man's temperature rose suddenly to 104 F, after a severe chill, and his condition rapidly changed to one of the utmost gravity. About forty hours later he was admitted to the hospital. The following record was made: "The patient was semicomatose, irrational and incontinent, with continual hiccough. The temperature was 103.4 F. He could be aroused to answer questions, but he promptly lapsed into toxic delirium. There was an ulcer on the tip of the left thumb, and the nodes in the left axilla were about 4 cm in diameter. There was no exanthem. Extreme miosis was noted. The patient was drowsy, his face was flushed and there was warm cyanosis. The liver and spleen were readily felt 3 fingerbreadths below the costal margin. Numerous rales were heard over the entire thorax, front and back. Pneumonic consolidations were noted at the base of both lungs." Sixty-six cubic centimeters of antitularia serum had no effect on the rapidly downward course, and death occurred on the seventeenth day of disease, six and one-half days after the onset of septicemia. The physical signs of pulmonary miliary tuberculosis were interpreted as miliary tularemic focal necroses. Necropsy was not permitted, but on clinical grounds death was clearly due to tularemic sepsis. The young woman, who was admitted to the hospital on the same day as her father-in-law, never became seriously ill. She received small doses of goat antiserum and made a prompt recovery.

There is a small final group of fatal cases not hitherto mentioned. Cases 19, 37, 61, 62 and 76 are illustrative. So far as is known all the patients were healthy prior to tularemic infection, and, with the exception of one patient (case 76), all apparently died of tularemia. Deaths occurred from the third to the ninth month of disease. Progressive extension of the tularemic process to the pleurae, pericardium, peritoneum, lungs and kidneys and their sequelae, empyema, pneumothorax, peritonitis, pulmonary abscess and nephritis, appeared to account for the deaths. It is remarkable how long active, progressive lesions can persist in a few instances. These are doubtless correctly correlated with the repeated relapses, febrile and symptomatic, and often with frank recrudescences of focal lesions, that recur persistently in a few instances, in some for as long as from five to nine years after the onset. In case 76 death was due to pulmonary miliary tuberculosis. It is possible that a tularemic lesion liquefied a quiescent tubercle and ushered its contents into the circulation. Necropsy was performed, and Dr. Calder kindly sent me sections of the lungs. Every miliary and submiliary tubercle

in the section stained with carbolfuchsin showed numerous typical tubercle bacilli. No other bacteria were seen. No lesions in the sections examined could be referred to tularemia.

A study of ages at death has not yielded any new information. The frequency distribution for single years is shown in chart 2. The same data, grouped according to decades, are shown in table 4. This tends to support a growing clinical prejudice that the infection is more serious after the fiftieth year, but the series is too small to be significant. There is no marked differential mortality between the sexes.

TABLE 4—*Frequency Distribution of Ages at Death, Grouped According to Decades*

Age, Years	Number of Deaths	Age, Years	Number of Deaths
0-9	5	40-49	15
10-19	2	50-59	18
20-29	9	60-69	16
30-39	18	70-79	1

SUMMARY

The chief cause of death attributable to tularemia alone is septicemia due to *Bact. tularensis*. Pneumonic lesions are present in about half the fatal cases of tularemia. Most cases of pneumonia that are associated with fatalities derive from the septicemia. Pneumonia that originates from the primary bacteremia does not become associated with fatalities unless septicemia supervenes. At least 70 per cent of the cases of tularemic pneumonia do not result in death. In a small number of patients, probably much smaller than the proportion in this series indicates, the primary bacteremia is septicemia from the onset and causes a rapidly fatal termination in from four to ten days. These unfortunate persons have apparently no natural resistance to the infection. The septicemia which causes most fatalities originates from a second invasion of the blood stream. Tularemic sepsis, with its consequent miliary focal necroses, may be generalized or may be limited to either the systemic or the pulmonary circulation. In this respect it is analogous to miliary tuberculosis. This analogy may be extended to the modes of origin of septicemia.

The mortality rate of the typhoid type of tularemia is four times that of the other clinical types. The incidence of pneumonia for this type is four times the average incidences in the three other types and is three times larger than the incidence of pneumonia in tularemia in general.

Tularemia is especially dangerous to persons with preexisting coronary heart disease. Death may occur in such cases from coronary occlu-

sion or acute myocardial failure during the initial acute phase or during early or late convalescence. The surviving patient may suffer attacks of angina pectoris, coronary occlusion and heart block for months or years after recovery from tularemia.

Persisting, progressive tularemic lesions which ultimately involve important structures are infrequent causes of death late in the course of the disease.

The third week of infection is the most dangerous period, and most deaths occur on the sixteenth day of illness. The disease is characterized by severe toxemia, which appears, of itself, seldom or never to cause death among patients who were healthy at the time tularemia was contracted. Persons over 50 years of age tolerate the infection less well than younger persons.

It is estimated that 4 of every 5 deaths from tularemia could have been prevented by the early administration of serum therapy.

PULMONARY INFARCTION COMPLICATING SEVERE DISEASE OF THE MITRAL VALVE

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An important and frequently fatal complication of severe mitral stenosis is pulmonary infarction, a complication at times difficult to diagnose and to a considerable degree neglected in medical writing. Though recognized for many years, the influence of this complication on the course of disease of the mitral valve, especially in the presence of marked congestive failure, is but little discussed in medical literature. Our attention has been recently attracted to its importance by 5 cases, 4 of the patients having been seen in the past year.

In our patients congestive heart failure, though mild at the onset, became progressively worse, and despite the therapeutic measures that were employed all 5 died within a comparatively short time. We do not think that this condition is rare, for 4 of our 5 patients were seen within a period of one year in one hospital, and we have recently encountered clinically several other patients for whom we believe the same diagnosis should have been made. One of the latter patients had marked jaundice, and although the presence of jaundice usually makes the outlook grave, this patient left the hospital in good condition.

The diagnosis of pulmonary infarction during life is not always easy, especially if there are symptoms and signs suggesting pulmonary consolidation of active rheumatic origin. The presence of pulmonary infarction should always be suspected if there is blood-streaked sputum. Also one may suspect infarction of the lungs, if congestive failure does not respond to general routine treatment, provided there are no other complications, such as masked hyperthyroidism, that may retard the effect of treatment. The presence of pulmonary infarction in severe disease of the mitral valve with congestive failure should be borne in mind as a possible contraindication for total thyroidectomy, for in these cases this radical procedure would be of no avail.

SURVEY OF THE LITERATURE

Most reports in the literature dealing with pulmonary embolism and infarction are those concerned with cases in which the condition followed a surgical procedure. Some of the reports deal with statistics

of the presence of pulmonary infarction in medical cases. There are also a few cases of pulmonary infarction in severe disease of the mitral valve.

Muller¹ has reported the interesting case of a woman aged 40 who died of pulmonary infarction after gangrene of the left leg due to peripheral embolism, at autopsy there was noted unsuspected mitral stenosis.

Schramm² reported the case of a woman aged 44 with massive thrombosis of the pulmonary artery in the presence of a very large heart with mitral stenosis. In his paper he summarized the data in 3 other cases reported in the literature in which there was mitral stenosis and 5 in which there was no mitral stenosis. He said he was of the opinion that in most of these cases the pulmonary infarction was of embolic origin.

Lutembacher³ reported 2 cases—that of a woman of 32 and that of a man of 36, in both of these cases there was “pure” mitral stenosis.

Fowler⁴ reported the case of a man of 52 with mitral stenosis and pulmonary infarction. It is interesting to note that in this case the diagnosis was masked by the symptoms of the primary disease. This feature was observed in 3 of our cases.

Billings,⁵ on the other hand, found reports of 16 cases of “primary” thrombosis of the pulmonary artery without mitral stenosis among the reports of 6,200 autopsies.

Boswell and Palmer⁶ reported a case of pulmonary infarction without any cardiac lesion as a result of primary thrombo-arteritis of the pulmonary artery. Interestingly enough, this patient had no episodes of sudden pain.

Frothingham⁷ reported a case of extensive bilateral progressive thrombosis of the smaller branches of the pulmonary artery.

1 Muller. Gangrene du membre inférieur gauche par embolie au cours d'un rétrécissement mitral latent, amputation précoce, mort par infarctus pulmonaire, constatations anatomo-pathologiques, *Loire med* **31** 321, 1912.

2 Schramm, H. G. Beitrag zur Aetiologie der Thrombose der Arteria pulmonalis, *Ztschr f Kreislaufforsch* **19** 713, 1927.

3 Lutembacher, R. Thrombose de la branche droite de l'artère pulmonaire, *Arch d mal du cœur* **26** 601, 1933.

4 Fowler, W. M. Obliterating Thrombosis of the Pulmonary Arteries, *Ann Int Med* **7** 1101, 1934.

5 Billings, F. T. Primary Thrombosis of Pulmonary Artery, *Pennsylvania M J* **25** 152, 1921.

6 Boswell, C. H., and Palmer, H. D. Progressive Thrombosis of the Pulmonary Artery, *Arch Int Med* **47** 799 (May) 1931.

7 Frothingham, C. Case of Extensive Bilateral Progressive Thrombosis of Smaller Branches of Pulmonary Arteries, *Am J Path* **5** 11, 1929.

Weiss and Davis⁸ found that in 9 of their 26 cases of fatal embolism in rheumatic heart disease there was marked congestive failure and in 17 there was slight or no congestive failure. They noted also in a series of 164 cases of rheumatic heart disease that the circulatory impairment often became intensified after embolism, while in some cases congestive failure developed after the accident of embolism. Pulmonary embolism and systemic embolism were not, however, differentiated.

Oberndorfer,⁹ in his report from a German clinic, showed that from 1912 to 1927 there had been a decided increase in the number of cases of pulmonary embolism and thrombosis. While in 1912 there were 30 per cent among the cases in which autopsy was performed as a routine, in 1927 there were 56 (44 per cent) among 128 medical cases in which autopsy was done. He discussed four possible reasons for such an increase, namely

- 1 Intravenous therapy (this etiologic factor is emphasized also by Rosenthal¹⁰) Oberndorfer said he thought this procedure, whatever influence it has on the course of the disease, serves as a possible factor in producing local changes either in the vessels of the arm or in the pulmonary circulation. There is little or no evidence, however, that phlebitis and venous thrombosis in the arms result in pulmonary embolism.

- 2 A late effect of the influenza epidemic of 1918

- 3 A late effect of malnutrition as a result of the World War

- 4 The greater longevity of persons with cardiac disease, due to improved therapeutic measures

The second and third reasons are remote and unlikely. A much more plausible theory is the fourth, namely, that of longevity of persons with cardiac disease, so far as they live longer because of improved therapeutic measures. These patients go in and out of congestive failure so often that peripheral and pulmonary thromboses are not infrequent sequelae.

Zink,¹¹ in his analysis of the reports of autopsies at the Freiburg Pathologic Institute from January 1926 to July 1930, has shown that among 54 cases of fatal pulmonary embolism there were 38 cases in which previous hemorrhagic infarction was noted and 45 cases of pul-

8 Weiss, S. and Davis, D. Rheumatic Heart Disease. III Embolic Manifestations, *Am Heart J* **9** 45, 1933.

9 Oberndorfer, S. Die Zunahme der Lungenembolien, *München med Wchnschr* **75** 683, 1928.

10 Rosenthal, S. R. Thrombosis and Fatal Pulmonary Embolism. Comparison of Their Frequency in the Clinics in Central Europe and North America, with Special Reference to Increase, *Arch Path* **14** 215 (Aug) 1932.

11 Zink, K. Der hamorrhagische Lungeninfarkt als Vorbote der tödlichen Lungenembolie, *Med Klin* **27** 1247, 1931.

monary stasis, in 9 cases there was no stasis of the pulmonary circulation. In this group of 9 cases no preceding infarction was observed. In his series, however, there were only 3 cases of mitral stenosis, and there were no comparative figures as to the frequency of pulmonary infarction in cases of hypertension.

Cabot,¹² in his observations in 200 cases of mitral stenosis, found 14 instances of embolism to various parts of the body, but he reported no cases of pulmonary infarction.

Belt,¹³ in his analysis of 567 autopsy reports, found 56 cases of pulmonary embolism, 40 of which were nonsurgical. In the latter group there were 12 cases of coronary disease, 9 cases of rheumatic heart disease, 2 cases of hypertensive heart disease, 1 case of syphilitic aortitis and 1 case of pericarditis. In all cases congestive failure was present. As to the possible etiology of thrombosis, his work indicated that infection played no part, but he stated as his conclusion that slowing of the blood stream, as reported by Blumgart and Weiss, was an important factor in favoring thrombosis. He also stated the opinion that pulmonary emboli are much more common than they are generally thought to be, especially small emboli that do not cause sudden death but that may be a seat for thrombosis. These may come from the deep veins of the leg and go unrecognized. Unless careful search is made, these small emboli and infarcts will not be found.

Sheppard¹⁴ cited Rupp, who in a statistical review of reports of 13,000 autopsies found 657 cases of pulmonary embolism and infarction of all forms and sources. In 248 of these 657 cases some kind of cardiac disease was present, but no special form was described.

Steuer,¹⁵ in his report of 25 cases of obstruction of the pulmonary artery, listed 19 cases of thrombosis and 6 cases of embolism. In the former group there were 16 cases of congestive failure. In 5 of the 19 cases of pulmonary thrombosis there was auricular fibrillation, there were 13 cases of hypertension, 1 case of rheumatic heart disease, 3 cases of cardiovascular syphilis and 2 of disease of the coronary arteries. Among the 19 cases of thrombosis there were 13 cases (68 per cent) of pulmonary infarct. Among the 6 cases of embolism, there were 3 cases of disease of the mitral valve, 1 case of hypertension, 1 of

12 Cabot, R. C. Mitral Stenosis. Observations on Two Hundred Cases Before and After Death, Also on One Hundred and Sixteen Not Autopsied. *Tr. A. Am. Physicians* **29** 22, 1914.

13 Belt, T. H. Thrombosis and Pulmonary Embolism, *Am. J. Path.* **10** 129, 1934.

14 Sheppard, T. T. Pulmonary Embolism and Infarction, *Atlantic M. J.* **27** 588, 1923.

15 Steuer, L. G. Embolism and Thrombosis of Large Branches of Pulmonary Artery in Heart Disease, *J. Lab. & Clin. Med.* **19** 265, 1933.

syphilis and 1 of disease of the coronary arteries. His conclusions were that hypertensive heart disease was most frequently associated with pulmonary thrombosis, while rheumatic heart disease was most frequently associated with pulmonary embolism. "In conclusion," he stated, "it can be said, that in a case of prolonged cardiac failure with repeated indications of pulmonary infarction, embolism or thrombosis of the pulmonary vessels may be anticipated."

Hosoi,¹⁶ in his analysis of 810 reports of necropsies from 1921 to 1929, found 64 cases of pulmonary embolism, 36 of which were medical cases. In the latter group there were 4 cases of congestive failure.

Farr and Spiegel¹⁷ from their study of 32 cases of pulmonary embolism with infarction between 1881 and 1927 concluded

1 In spite of stasis, which in some cases is generalized, primary thrombosis in the peripheral veins as a source of pulmonary infarction is rare. They noted only 1 case in which the veins of the leg may have been the source.

2 Pulmonary infarction is not necessarily embolic. Passive congestion plays an important rôle.

Farr and Spiegel further stated that the pulmonary involvement plays but a minor part in the severity of the condition but is of prognostic value because it reflects the extent of the failure of the right side of the heart. In their series there were 22 cases of cardiovascular origin, but no mention was made either of congestive failure or of what valves were involved.

Two clinical pictures of pulmonary infarction have been described in the textbooks and recently emphasized by Sheppard¹⁴. In one there is a sudden episode of sharp pain in the chest followed by hemoptysis. This type may occur in severe disease of the mitral valve, with or without congestive failure. If congestive failure is not present, a satisfactory recovery is frequently made. Examination usually reveals evidence of consolidation, and not infrequently this is mistaken for lobar pneumonia. In a great majority of cases a pleural friction rub is heard, and this is considered by many to be a part of the pneumococcal infection. Not infrequently one may find such an episode in the presence of congestive failure. In these instances the diagnosis is not difficult.

The second type that has been described occurs in severe disease of the mitral valve with congestive failure and consists of a sudden severe attack of hemoptysis, with or without ensuing pain in the chest. Occasionally one will encounter a case in which there is severe pulmonary edema but little evidence of consolidation, as in the previous type.

16 Hosoi, K. Pulmonary Embolism and Infarction. Analysis of Sixty-Four Verified Cases, *Ann Surg* **95** 67, 1932.

17 Farr, C. E., and Spiegel, R. Pulmonary Infarction and Embolism. *Ann Surg* **89** 481, 1929.

Although pulmonary infarction is frequently considered to be of embolic origin there are numerous instances in which local changes in the pulmonary arteries are the only positive findings

REPORT OF CASES OF PULMONARY INFARCTION COMPLICATING DISEASE OF THE MITRAL VALVE WITH CONGESTIVE FAILURE

In 4 of our 5 cases there was no history of hemoptysis at any time, while in the fifth case, though there was a history of hemoptysis several years prior to the onset of the present illness, when congestive failure set in there was no evidence of hemoptysis. The main feature in all our cases was the impossibility of controlling the increasing congestive failure. The difficulty of making the diagnosis of pulmonary infarction in such cases is due to the fact that the cardiac symptoms overshadow those due to the infarction. Occasionally the pulmonary symptoms are so severe that unsuspected mitral stenosis is overlooked, as in the case reported by Muller¹

In 3 of our 5 cases there was a normal cardiac rhythm and in 2 auricular fibrillation, interestingly, in none of these 5 cases was there evidence of a thrombus in the heart at postmortem examination. There was suggestive evidence of active rheumatic heart disease in 2 cases, while in the other 3 there was no evidence of such activity. All 5 patients were women, their ages were 36, 41, 19, 51 and 29 years, respectively

CASE 1—Mrs E. van D., aged 36 years, entered the hospital on Sept. 6, 1934, and died on October 14. The family history was unimportant. There was no history of rheumatic fever. Curettement of the uterus was performed in 1930 and in 1932. There had been increasing dyspnea since the spring of 1932 and swelling of the feet and abdomen for the past month. There had also been a dry cough for two years without hemoptysis.

On physical examination there were a low-pitched rumble throughout diastole, a sharp first sound at the apex of the heart and moderate engorgement and pulsation of the cervical veins. The cardiac rhythm was normal. There was dulness at the base of both lungs, with moist râles up to the midcapsular region. The liver was enlarged and tender. The abdomen was tender, with dulness in the iliac region. There was edema of the abdominal wall and of the sacrum.

Course—The congestive failure gradually yielded to the effect of digitalis and diuretic drugs, and the patient was entirely free from edema when she began to suffer from gradually increasing dyspnea, with fever leading to death in a few days. Dulness and bronchial breathing were noted at the base of the right lung.

Diagnosis—The clinical diagnosis was rheumatic heart disease, mitral stenosis and pulmonary infarction.

Postmortem Examination—At autopsy the heart showed much enlargement of the right ventricle and left auricle, with increased thickness of the walls. The pulmonary artery was free. There was no pericarditis or acute endocarditis. No Aschoff bodies were seen. There were no thrombi in the auricles. The left lung

was normal. The right lung was infarcted, the infarct involving three quarters of the lower lobe and one third of the middle lobe. The infarct in the lower lobe extended 11 cm upward from the diaphragmatic surface in back and 4.5 cm upward from the diaphragmatic surface in front. The infarct in the middle lobe was in the lateral part. There was bronchopneumonia around the infarcted areas. There was an adherent thrombus in the artery to the lower lobe of the right lung, with slight change in the wall of the artery at the distal end of the thrombus and an extension of the thrombus back several centimeters to include the whole of the blood supply to the lower lobe and part of that to the middle lobe.

CASE 2—Miss J. E. J., 41 years of age, a teacher entered the hospital on Feb. 11, 1935, and died on February 14. The family history was unimportant. The patient was first seen by one of us in 1932, and examination then showed mitral stenosis. There was slight cardiac enlargement, the presence of which was proved by roentgenograms. She was well until two weeks before entrance to the hospital, when sore throat developed with a temperature of 101 to 102 F. There was no cough or hemoptysis.

Physical examination revealed evidence of consolidation of the lower lobe of the right lung, with some congestive failure, as shown by hepatic engorgement and distention of the cervical veins. The cardiac rhythm was normal. There was marked mitral stenosis.

Course—Three days after the patient's entrance to the hospital there were rales and bronchial breathing in the left axilla, but no friction rub. There was increasing edema before death.

Diagnosis—The clinical diagnosis was rheumatic heart disease, mitral stenosis and (?) rheumatic pneumonia.

Postmortem Examination—At autopsy there was slight enlargement of the heart (weight, 350 Gm.). The right ventricle was markedly hypertrophied and dilated. The mitral valve was markedly stenosed, with short chordae tendineae, and there was a question of fresh vegetations on the aortic valve. The pericardium showed several hemorrhagic spots over the anterior surface near the interventricular sulcus. There were no thrombi in the auricles. The lungs showed six or eight hemorrhagic infarcts, with thrombosis of the pulmonary vessels leading to them in at least 2 instances. Grossly the vessels were normal.

Microscopically no Aschoff bodies were seen in the myocardium, but in a section of the mitral valve at the base there was seen a collection of cells having rare vesicular nuclei, similar to plasma cells, constituting a focus which was thought to be an Aschoff body.

CASE 3—Miss B. M., aged 19 years, entered the hospital on Dec. 6, 1934, and died on December 10. The family history was unimportant. There was no history of rheumatic fever. Tonsillectomy had been performed in 1929.

For seven years before her entrance to the hospital, during routine examinations at school, she was told she had a heart murmur. During the summer of 1934 she had an attack of coughing. In August, while swimming, she had an attack of palpitation which was apparently due to auricular fibrillation, with a heart rate of 120 to 130. The fibrillation persisted in spite of the use of digitalis, without change in the heart rate, except on one occasion, when it dropped to 80.

Physical examination on November 27 at her home showed evidence of slight arterial pulsation in the neck. The heart was markedly enlarged to the left and downward. The rhythm was irregular. There were present the murmurs of mitral

stenosis and regurgitation. The lungs were clear. Examination of the abdomen revealed that the edge of the liver was palpable 2 fingerbreadths below the costal margin. There was no dependent edema.

Course—On December 6 the patient's condition became much worse, the heart rate rose to 140 or more and the temperature to 104 F. Gradually there was increasing congestive failure, and she died on December 10.

Postmortem Examination—Autopsy showed enlargement of the heart due to hypertrophy and dilatation. The heart weighed 325 Gm. All the valves were normal, except the mitral valve, which was deformed but not stenosed. There were short chordae tendineae and thickening of the line of closure and at the edge of the valve. There were no antemortem intracardiac clots. There were no vegetations. Over the pericardium, pleurae and peritoneum there were several small hemorrhagic areas, and in the right lung there were several areas of hemorrhagic consolidation, resulting in a diagnosis of pulmonary infarct (?) and rheumatic pneumonia (?).

Microscopic examination showed that the vessels throughout the myocardium were markedly congested. There were a few foci where the muscle fibers were fragmented and often replaced by a homogeneous, pink-staining substance over which there were a few oval nuclei without any cell membrane. Around some of the larger vessels there was an occasional but only slightly suggestive Aschoff body.

CASE 4—Miss M. W., aged 51 years, entered the hospital on May 2, 1934, and died on May 14.

Her complaint was of constricting pain in the upper portion of the abdomen of six years' duration and more recent orthopnea. She had had rheumatic fever every winter when between the ages of 3 and 14 years. There had been discomfort in the upper portion of the abdomen for the past six years, and there had been increasing dyspnea for two or three years. The heart beat had been irregular since 1930, at which time she was in bed for seven weeks. She had been taking digitalis since 1931. There was a slight cough, brought on by the dyspnea. In May 1931 an examination showed a blood pressure of 150 systolic and 100 diastolic, auricular fibrillation (with a ventricular rate of 80), a rumbling mid-diastolic and a late diastolic murmur at the apex and fine moist râles at the base of the right lung.

Physical examination on May 2, 1934, showed a blood pressure of 140 systolic and 90 diastolic, a heart rate at the apex of 92 and a radial pulse rate of 84. The heart was described as noted previously. Examination revealed some pleural fluid at the base of the right lung. The liver was very tender and extended 4 or 5 fingerbreadths below the costal margin. There was cyanosis of the lips, with pallor of the nails.

Course—There were increasing edema and dyspnea, despite the use of diuretics. The patient died on May 14.

Postmortem Examination—At autopsy the mitral valve was markedly calcified and thickened, with a fish mouth opening 2 cm in length. There were two pulmonary infarcts. The pleural surfaces were mottled blue and gray, except for an irregular area in the lower lobe of the left lung, which was dark red, and a small rounded area in the anterior surface of the upper lobe of the right lung, which also was dark red. The lower lobe of the left lung showed a roughly cone-shaped area which was firm and reddish black, about 4 cm in diameter at its base and 5 cm in height. The upper lobe of the right lung showed another cone-shaped firm area, 1.5 cm in diameter at the base and 2 cm in height.

CASE 5—J R, a woman, aged 29 years, entered the hospital on Dec 1, 1931, and died on December 4

Her father had died of disease of the coronary arteries Her past history was unimportant, except for "growing pains" in childhood

For nine years prior to entrance to the hospital the patient had coughed up blood on several occasions, but at no time was there congestive failure, until six months before her admission to the hospital, when edema of the legs was first noticed There was no hemoptysis after the onset of congestive failure There was also a nonproductive cough

Physical examination revealed cyanosis and orthopnea There were mid-diastolic and presystolic murmurs at the apex of the heart There was marked cardiac enlargement There were impaired resonance over the base of the right lung, bronchovesicular breathing on the right in the middle of the back, distant breathing at the base of the right lung and a few râles at the base of each lung

Course—Digitalis and salyrgan had no effect on the increasing edema Death occurred three days after the patient's entrance to the hospital

Postmortem Examination—Autopsy showed the right ventricle to be dilated The heart weighed 500 Gm There were no fresh vegetations on the mitral valve, but there were some on the atrial side of the tricuspid valve No Aschoff bodies were present in the myocardium The visceral and parietal surfaces of the pericardium showed many petechial spots There were areas of infarction in the upper and lower lobes of the right lung, as well as a few smaller nodules in the periphery of the lower lobe of the left lung The right pulmonary artery contained an elongated, ragged, red antemortem clot progressively filling the lumens of several of the smaller branches of the pulmonary artery The upper three quarters of the upper lobe and the upper half of the lower lobe of the right lung, as well as two distinct small areas in the lower lobe of the left lung, were infarcted

STATISTICAL STUDY OF THE INCIDENCE OF PULMONARY INFARCTION IN DISEASE OF THE MITRAL VALVE AT THE MASSACHUSETTS GENERAL HOSPITAL

To determine the frequency of pulmonary infarction in severe disease of the mitral valve, all the cases in which autopsy was performed at the Massachusetts General Hospital over a period of fifteen years and in which a diagnosis of mitral stenosis was made were investigated, and a comparative study was made with cases in which the diagnosis was hypertensive heart disease The accompanying tables show how frequently mitral stenosis is complicated by pulmonary infarction It will be noted that in 23 of the 52 cases of severe mitral stenosis there was congestive failure In this group of 23 cases there were 14 (61 per cent) in which pulmonary infarction was a complication, while in 9 (39 per cent) there was no infarction There were 27 cases of mitral stenosis without congestive failure and without infarction In 2 cases there was no congestive failure with infarction These 52 instances were found in the records of 2 500 autopsies performed between 1919 and 1934

In the records of 1,400 autopsies performed from 1930 to 1934 there were 82 cases of hypertension. In 39 of the 82 cases there was congestive failure, in 8 cases (21 per cent) infarction being present, as compared with 61 per cent for the cases of rheumatic heart disease. Thus there were 31 cases (79 per cent) of congestive failure without infarction. In the 43 remaining cases in which congestive failure was not present, there were 5 cases of pulmonary infarction and 38 cases in which there was no infarction.

TABLE 1—*Cases of Mitral Stenosis Among the Records of 2,500 Autopsies at the Massachusetts General Hospital, 1919 to 1934*

	No. of Cases	Percentage
Mitral stenosis and congestive failure with pulmonary infarction	14	61
Mitral stenosis and congestive failure without pulmonary infarction	9	39
Mitral stenosis without congestive failure and with pulmonary infarction	2	7
Mitral stenosis without congestive failure and without pulmonary infarction	27	93
	—	
	52	

TABLE 2—*Cases of Hypertension Among the Records of 1,400 Autopsies at the Massachusetts General Hospital, 1930 to 1934*

	No. of Cases	Percentage
Hypertensive heart disease and congestive failure with pulmonary infarction	8	21
Hypertensive heart disease and congestive failure without pulmonary infarction	31	79
Hypertensive heart disease without failure and with pulmonary infarction	5	12
Hypertensive heart disease without congestive failure and without pulmonary infarction	38	88
	—	
	82	

COMMENT

Pulmonary infarction as a complication of severe disease of the mitral valve, especially in the presence of congestive failure, is not infrequent, as shown by the statistics in the accompanying tables. Four of the 5 new cases reported were discovered by us in the course of one year, and doubtless in more cases this diagnosis would have been made had an autopsy been performed.

It is important to recognize this complication, not only from the standpoint of greater diagnostic accuracy but because its recognition indicates with a fair degree of certainty that the prognosis is grave.

Although in the 5 cases reported here the outcome was fatal, we have noted cases in which the patient recovered, including even a recent case

in which there was considerable jaundice, usually a grave sign. Jaundice, when it does occur in these cases, is of hemolytic nature, due to the sudden excessive burden on a congested and perhaps otherwise damaged liver of disposing of the large amount of blood pigment in the pulmonary infarct.

The presence of pulmonary infarction retards all forms of treatment for congestive heart failure.

There are four possible sources of pulmonary infarction.

1. Thrombosis *in situ* may be the source. This may be favored by such pulmonary arteriosclerosis as was noted by Brenner¹⁸ in his study of the pathology of the pulmonary circulation, which is almost certainly favored by the sluggish circulation in the dilated pulmonary vascular system. With increasing congestive failure in cases of mitral stenosis, resulting in a sluggish and engorged pulmonary circulation, it is possible for a thrombus to form in the pulmonary arterial system. After this sequence, pulmonary infarction is likely to take place.

2. Embolism from concealed thrombosis in veins of the abdomen, pelvis or legs, as shown by Homans,¹⁹ is another possible source of pulmonary embolism. The search for emboli in the veins of the legs as a possible source is a tedious process, and on this continent a thorough search is rarely made, not infrequently cases are overlooked, and the source of the pulmonary infarction is undetermined.

3. Embolism from thrombi in the chambers of the right side of the heart is prone to occur, especially in the presence of auricular fibrillation. This is particularly true when the circulation has been greatly retarded. However, in our series, although in 2 cases auricular fibrillation had been noted, none of the hearts showed any evidence of thrombi in the auricles or ventricles at autopsy.

4. Acute infection superimposed on an old rheumatic lesion may be a possible source of pulmonary infarction, especially in younger persons. In 2 of our cases there were structures suggestive of Aschoff bodies in the cardiac valves, indicating the location of the possible source. This theory was emphasized in 1858 by de Zumann, as quoted by Giroux.²⁰

18 Brenner, O. Pathology of the Vessels of the Pulmonary Circulation, *Arch. Int. Med.* **56** 211 (Aug.), 547 (Sept.), 724 (Oct.), 976 (Nov.), 1189 (Dec.) 1935.

19 Homans, J. Thrombosis of Deep Veins of Lower Leg Causing Pulmonary Embolism, *New England J. Med.* **211** 993, 1934.

20 Giroux, L. Sclérose et athérome de l'artère pulmonaire, rôle des conditions mécaniques, Thèse de Paris, no 149, Paris, G. Steinheil, 1910.

Pulmonary infarction as a clinical picture presented in our series of 5 cases has not been well recognized as such—that is, a clinical picture of intractable pulmonary embarrassment without any sudden episode in the presence of severe disease of the mitral valve and congestive failure. This type of complication may or may not be accompanied with evidence of pleural friction. One should always bear in mind that in these cases the clinical syndrome of a sudden vascular accident is not necessary for the diagnosis of pulmonary infarction.

SUMMARY AND CONCLUSIONS

We report here 5 cases of severe disease of the mitral valve with congestive failure having as a fatal complication pulmonary infarction without any clinical syndrome of sudden vascular collapse or any similar episode. Autopsy was performed in each case.

Analysis of the incidence of this complication in a series of 52 cases of mitral stenosis noted in 2,500 records of autopsies at the Massachusetts General Hospital showed that pulmonary infarction occurred in 61 per cent of 23 cases in which there was congestive failure and in only 7 per cent of the cases in which congestive failure was not present. In a comparative group of 82 cases of hypertension noted in the records of 1,400 autopsies at the Massachusetts General Hospital, there were 39 cases of congestive failure, in 21 per cent of which there was pulmonary infarction.

Pulmonary infarction complicating severe disease of the mitral valve with congestive failure is not uncommon. This condition is sometimes difficult to diagnose, it makes treatment of the congestion very difficult, and it renders the prognosis grave.

MONOCYTIC LEUKEMIA

CUTANEOUS MANIFESTATIONS OF THE NAEGELI AND SCHILLING TYPES, HEMOCYTOLOGIC DIFFERENTIATION

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AND

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It is important to distinguish between the so-called Naegeli type of monocytic leukemia (which many regard as a variant of myelogenous leukemia, with predominance of monocytes) and the true Schilling type (leukemic reticulo-endotheliosis), in which the cells are derived from the reticular cell. A primary autochthonous cutaneous origin for either type of monocytic leukemia may be encountered, a fact which we believe is not generally recognized by internists and pathologists or even by many dermatologists. One of us (H M)¹ has previously emphasized the possible autochthonous cutaneous origin of any of the lymphoblastomas, including even myelogenous leukemia.²

It is not pertinent in this paper to discuss the various hemocytologic views regarding the monovalent, dualistic and trivalent origin of leukocytes.³ There is an increasing tendency in the recent literature to recognize two types of monocytic leukemia as well as the lymphatic and myelogenous types of leukemia. If one accepts the point of view that

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1 Goeckerman, W H, and Montgomery, Hamilton. Cutaneous Lymphoblastoma. Report of Two Unusual Cases, *Arch Dermat & Syph* **24** 383-395 (Sept) 1931. Montgomery, Hamilton. Exfoliative Dermatitis and Malignant Erythroderma. The Value and Limitations of Histopathologic Studies, *ibid* **27** 253-271 (Feb) 1933. Mycosis Fungoides, Lymphoblastoma of the Skin, and Allied Conditions as General Diseases, in Christian, H A, and Mackenzie, J. *Oxford Medicine*, New York, Oxford University Press, 1936, vol 4, pt 1, chap 1A, pp 44(1)-44(19).

2 Barney, R E. Leukemic Myelosis Associated with Specific Nodules in the Skin. Report of a Case and Review of the Literature, *Arch Dermat & Syph* **27** 725-738 (May) 1933.

3 Kracke, R R, and Garver, Hortense. The Differential Diagnosis of the Leukemic States, with Particular Reference to the Immature Cell Types, *J A M A* **104** 697-702 (March 2) 1935. Wiseman, B K. The Origin of the White Blood Cells, *ibid* **103** 1524-1529 (Nov 17) 1934. Wiseman, B K, Doan, C A, and Erf, L A. A Fundamental, Reciprocal Relationship Between Myeloid and Lymphoid Tissues. Its Recognition, Nature and Importance as Revealed by Experimental and Clinical Studies, *ibid* **106** 609-614 (Feb 22) 1936.

reticular cells (reticulo-endothelial cells) and monocytes can give rise to lymphocytes then all the aforementioned conditions and also mycosis fungoides may be grouped under the term lymphoblastoma, with recognition of the fact that it is important to distinguish between these different types until more is known regarding their etiology

We wish to report five cases of monocytic leukemia with cutaneous manifestations, two of the Naegeli and three of the Schilling type. Primary autochthonous cutaneous involvement occurred in one or possibly two cases of the Schilling type and in one case of the Naegeli type as contrasted with secondary terminal cutaneous lesions in the other two cases one of each type

NAEGELI TYPE

CASE 1—A man aged 45 was first seen at the clinic in 1921, because of gastric distress for thirty years. Thorough examination failed to reveal any organic cause for his complaints. He was reexamined in August 1924, at which time a diagnosis of probable duodenal ulcer was made.

When the patient was seen for a third time, in 1928, the diagnosis was chronic nervous exhaustion, constipation and functional dyspepsia. The results of laboratory examinations were all within normal limits. The patient at this time complained of eczema of six weeks' duration, which had begun on the legs and had soon become generalized. Biopsy of one of the lesions from the shoulder revealed a dense infiltrate with many reticulum cells and other features of lymphoblastoma, although the picture was not diagnostic as to type. There was nothing abnormal about the hemocytologic picture.³ Roentgen treatment was given over the neck, mediastinum, pelvis, back and groins.

The patient returned to the clinic again in March 1929, at which time the plaques on the skin were more infiltrated and the picture was more suggestive clinically of mycosis fungoides. Another biopsy revealed a greater degree of infiltration, with multiplicity of cell types. There were also many lymphocytes and occasional monocytes and endothelial cells. There was a definite increase in reticulum (*Gitterfasern*, or lattice fibers). The histopathologic picture was not specific as to the type of lymphoblastomatous involvement. Further roentgen treatment was administered.

We saw the patient again in April 1932, when he had two plaques in the left pectoral region and one on the left forearm. Nodular infiltrations and necrotic ulcers also were present (fig 1). Biopsy at this time revealed a more active process, with a number of mitotic figures, so that both Dr Broders and one of us (H. M.) favored the diagnosis of mycosis fungoides bordering on lymphosarcoma. There was a definite increase in the number of monocytes and reticulum cells but no more than one would expect to see in a case of mycosis fungoides. The hemocytologic observations were again within normal limits. Additional roentgen treatment was given.

The patient returned to the clinic once more, in September 1932, at which time the condition of the skin was much improved. He had, however, lost 15 pounds (68 Kg). He had had recurring attacks of conjunctivitis and painful swelling, with local heat and fever in various parts of the body. He was hoarse, and there were edema and redness of the vocal cords which epinephrine did not relieve. Roentgenograms of the thorax, stomach and skull were normal, and blood cultures

were sterile. The hemocytologic observations were as follows: marked poikilocytosis, much basophilic stippling, an occasional normoblast and definite immaturity in the myeloid line back to the myeloblast or stem cell, with predominance of differentiation along the monocytic line. It was suggested that the condition was probably monocytic leukemia.

The patient was given a blood transfusion and experienced a subsequent febrile delayed reaction. The value for serum bilirubin and tests of hepatic function were normal. Prostatitis of grade 3 was present. Studies of the blood later in September revealed severe anemia, with the number of normoblasts increased over



Fig 1 (case 1) —Nodules and necrotic ulcers on the forearm and chest

that of the previous smear, more immaturity and more marked predominance of monocytes, with all stages of differentiation from the myeloblast or stem cells. A diagnosis of monocytic leukemia of the Naegeli type was thus established. Further hemocytologic studies confirmed these observations. Unfortunately no specimen of skin was taken for biopsy at this time, nor were specimens from the bone marrow or the costal cartilage examined. The patient went downhill rapidly and lost weight, and there was evidence of progression of the anemia. The spleen could not be felt, and there was no enlargement of the lymph nodes. Recurring areas of inflammation were present in the extremities, conjunctiva and chest, as well as hemorrhagic lesions. Pericardial friction rub, stupor and urinary reten-

tion developed, and the patient died on October 24. Postmortem examination confirmed the diagnosis of monocytic leukemia of the Naegeli type. There were fibrinous pericarditis and terminal bronchopneumonia, but the infiltrate in the lungs was composed chiefly of monocytic cells rather than leukocytes. There was grade 4 proliferation of the mediastinal nodes, and numerous monocytes were present. The spleen showed proliferation of reticulo-endothelial cells and numerous monocytes. The mesenteric nodes revealed hyperplasia of grade 3. The bone marrow contained large numbers of mature and immature neutrophils, myelocytes, monocytes and eosinophils.

CASE 2—A man aged 51 was examined at the clinic in September 1929, because of an enlarged lymph node in the neck, which had been present for six weeks. He had influenza in December 1928, but the gums remained sore, and pain developed in the chest and back. In March he began to become weak on exertion. Tonsillectomy was performed five weeks before his admission to the clinic, and afterward the lymph nodes became enlarged.

Examination revealed hypertrophy of the gums, mucous membranes and soft palate, the palate being swollen and edematous. All the lymph nodes in the neck were enlarged, tender, discrete and movable. The liver was palpable 4 cm below the costal margin, the spleen, too, was palpable. There was paralysis of the left side of the face (Bell's palsy) and a fading purpuric eruption limited to the thighs and legs but no infiltration suggesting leukemids. The patient was hospitalized. The hemocytologic observations were as follows: marked poikilocytosis, with much basophilic stippling, increased regenerative activity, definite myeloid immaturity back to the stem cell and marked predominance of monocytes. This was the picture of monocytic leukemia of the Naegeli type.

A month later the patient presented small nodular lesions, subacutely inflamed, which were limited to the right thigh and both shins, these strongly suggested leukaemia cutis. Biopsy revealed a definitely lymphoblastomatous picture, there being many large immature cells and also many monocytes. There was no evidence of lymphosarcoma or Hodgkin's disease. The patient died at home, and some of the organs were sent to the clinic for examination. Pathologic examination revealed marked hyperplasia of the bone marrow, myeloblasts and monocytes predominating. Numerous mitotic figures were present, indicative of an active process. There was no increase in free reticular cells. A similar picture was seen in a clot in the portal vein, in the splenic pulp and in the sinuses of a lymph node. The lymphoid tissue was not hyperplastic.

SCHILLING TYPE

CASE 3—A retired butcher aged 62 was first seen at the clinic on April 8, 1935, because of a cutaneous condition which had begun in March 1931 with itching on the inner aspect of the thigh and on the flexural surface of the arm. The hands had become involved in the summer of 1931 and the feet in 1932. The process extended to the flexures and volar surfaces of the forearms and the mesial aspects of the thighs. The extent and severity of the eruption had fluctuated, but the condition had never cleared up entirely.

Examination at the clinic revealed generalized thickening and lichenification of the skin and dry eczematous patches. The palms and soles showed marked hyperkeratotic scaling processes, with fissuring and heaping up under the free edge of the nails. There was definite lymphadenopathy in the groin. A diagnosis of mycosis fungoides was made, and a specimen for biopsy was taken from the plaque near the axilla. The histopathologic picture had many of the features of mycosis

fungoides (fig 2A), but later review of the sections revealed that a few of the lymphocyte-like cells presented notched serration and also grooving of the nuclei. The hemocytologic picture was similar, but there was insufficient evidence to

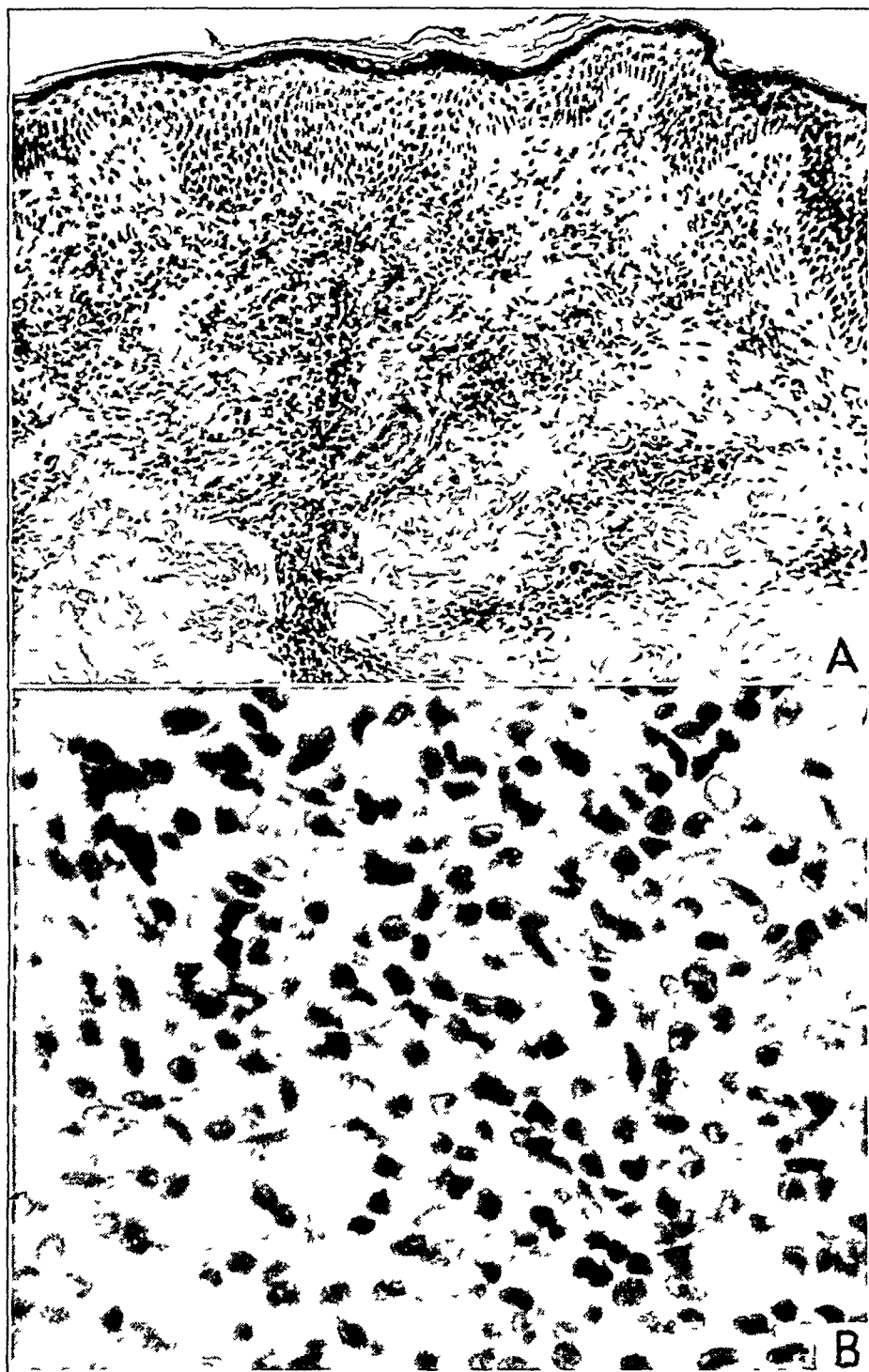


Fig 2 (case 3) —A, the histologic picture suggests mycosis fungoides (April 1935) B, the specific infiltrate in the skin of monocytic cells, many of which show definite grooving or serrated indentation of their nuclei (June 1936)

establish a diagnosis of monocytic leukemia of the Schilling type² Smears made from the specimen taken for biopsy and blood smears also revealed identical pictures. There was an increase in *Gitterfasern* in the specimen of skin. Roent-

genograms of the thorax as well as a general examination revealed no abnormality. The patient was given a course of roentgen therapy, and he obtained considerable relief from the itching.

The patient returned in June 1936, at which time he presented more the clinical picture of exfoliative dermatitis (fig 3). He had had eight roentgen treatments at home the last one in February. A specimen taken for biopsy revealed a some-



Fig 3—*A*, marked exfoliative dermatitis, later becoming erythroderma (case 3). *B*, the extent of the purpuric lesions throughout the skin of the entire body (case 5).

what denser infiltrate, with many definitely monocytic cells (of the Schilling type), both with indentations of nuclei and also with grooving through the nuclei (fig 2*B*). No clumping of cells, pyknosis or karyorrhexis of individual cells, such as characterizes mycosis fungoides, was seen in the second specimen for biopsy. The hemocytologic observations were as follows: leukemic reticulo-endo-

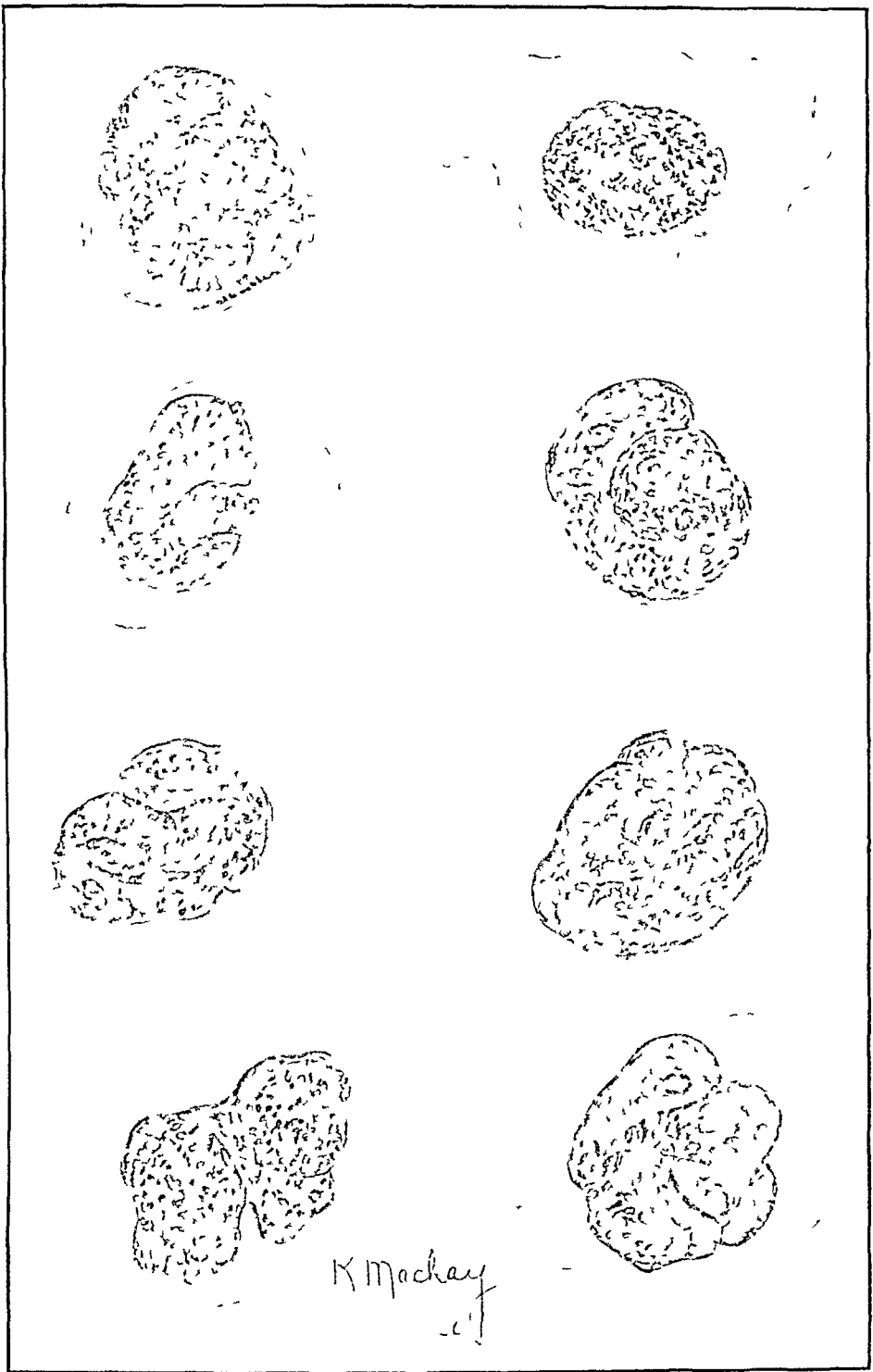


Fig 4—The difference between the various types of cells in monocytic leukemia. The left column, Naegeli type, from top to bottom illustrates the changes from the myeloblast to the relatively mature monocyte. The right column, Schilling type, represents stages in the development from the reticular cell to the mature monocyte.

theliosis, with monocytes showing definite grooving and intermediate stages of development back to primitive cells, with characteristics of the reticular cell. A diagnosis of monocytic leukemia of the Schilling type was made. On September 13 the patient was presented before the Mississippi Valley Dermatological Society. He then had mild, generalized residual erythroderma. There was no scaling. There had been remarkable improvement following roentgen treatment. No further laboratory studies were made at this time.

CASE 4—An unmarried woman aged 29 came to the clinic on April 13, 1935, because of generalized exfoliative dermatitis, which had begun in the fall of 1932 in the form of dryness and roughness of the palms and fingers. In a few months this condition had extended up the lower part of the arms and legs and by April 1933 had become exfoliative dermatitis. The patient was seen by various physicians and received roentgen treatment. In August 1933 a diagnosis of leukemia of the skin was made by Dr. Oliver S. Ormsby, but in November 1933 biopsy of a lymph node failed to reveal any evidence of a lymphoblastic process. The patient remained under the care of various physicians and received injections of a gold compound, further roentgen treatment and typhoid vaccine. When she was seen by Dr. H. R. Foerster in Milwaukee in April 1934 a diagnosis of lymphatic leukemia was made on the basis of a leukocyte count of 18,500 per cubic millimeter of blood, 59 per cent of the cells were reported as being of the lymphocytic series and 41 per cent as polymorphonuclear leukocytes. Biopsy of tissue from the forearm revealed a lymphoblastomatous picture, but it suggested the possibility of cutaneous Hodgkin's disease more than leukemia. Temporary improvement followed further roentgen treatment in conjunction with the administration of pills containing arsenic trioxide.

Examination at the clinic in April 1935 revealed generalized exfoliative dermatitis, only the skin of the face remaining free. There was a general brownish pigmentation of the skin, and a few more deeply pigmented macules were present, some of which may have been caused by roentgen or arsenic therapy. There were no keratoses on the palms or soles. Definite purpuric spots were present on the buccal mucous membrane and a few also on the trunk. The patient complained of the most intense pruritus. She had lost 15 pounds (6.8 Kg.) in the preceding few months. Studies of the blood revealed the following picture: a predominance of leukocytes with the definite characteristics of reticular cells, being about equally divided between lymphocytes and monocytes, an occasional very immature cell was present which exhibited the features of the reticular cells. A diagnosis was made of reticulo-endotheliosis of the Schilling type. Touch smears from the specimen for biopsy presented a picture identical with that of the blood smears. Biopsy revealed a definite lymphoblastomatous infiltrate in the upper portion of the cutis, containing many grooved monocytes and others showing notched serration of the nuclei. This supported the diagnosis of monocytic leukemia of the Schilling type (leukemic reticulosis). The majority of the cells were larger than those seen in chronic lymphatic leukemia.

The patient returned to Milwaukee and had further roentgen treatment and injections of ethyl chaulmoograte. She then went to her home in Fort Wayne, Ind., from which city Dr. W. W. Duemling wrote us in October 1936 that there had been a gradual increase in the leukocyte count, which then was 170,000 per cubic millimeter, 95 per cent of the cells being of the lymphocytic series. The patient still presented the picture of exfoliative dermatitis, but the lymph nodes were smaller. Her general health remained good. She has had further roentgen treatments and injections of ethyl chaulmoograte as well as arsenic trioxide.

The blood smears which Dr Duemling forwarded to us revealed the picture of chronic lymphatic leukemia. In addition there were many grooved cells of the reticulum series in other words, cells presenting all the morphologic features of monocytic cells of the Schilling type. These cells, however, were not as numerous as they were in the smears made when the patient was at the clinic in April 1935.

CASE 5—The patient, a man aged 68, was first seen at the clinic on Sept 24, 1935, because of extensive purpura involving the trunk and extremities (fig 3 B). He first noticed a number of brownish-purplish spots on his face in April. These were treated with ultraviolet radiation, with good results for ten days. They then recurred and gradually became more extensive. By July the purpura had become generalized, and the patient had become weak. In August he noticed lumps on the sides of his neck and in the axilla and groin. In September he received two transfusions of blood of 500 cc each. There was no change in his general condition, and he was sent to the clinic for diagnosis of the disorder.

Examination revealed extreme generalized ecchymoses and purpura of the skin, with generalized adenopathy and enlargement of the spleen and liver, the spleen extending 8 cm below the left costal margin and the liver descending below the right costal margin. A specimen for biopsy was not taken because of the danger that the wound would not heal and because the diagnosis could be, and was, made by means of hemocytologic studies. Otherwise, the general examination, including roentgenographic examination of the skull and femur, revealed no abnormality. Urinalysis did not reveal the presence of arsenic or lead. Examination of the blood revealed more or less acute monocytic leukemia of the Schilling type. Many very immature cells of the reticular type, with intermediate stages to practically mature monocytes, were present, but the predominant cell was immature. It is interesting that indentation of the nucleus was present in the extremely young reticular cells and was not a later development, as in the usual monocyte. There was secondary anemia, with some decrease in the number of blood platelets, but there was nothing special so far as the erythrocyte picture was concerned.

Roentgen treatment was given but without benefit, in fact, a greater degree of anemia developed. A blood transfusion was given. The patient's general condition improved somewhat, the adenopathy grew less marked and he was sent home on October 9. The prognosis was guarded. The patient died on Feb 22, 1936. No postmortem examination was made.

HEMOCYTOLOGY

The Naegeli type of monocytic leukemia may be definitely distinguished from the Schilling type on the basis of hemocytologic studies.⁴ There is a tendency among hematologists to separate monocytic leukemia into two types according to derivation of the predominant cell and also according to the distinguishing morphologic characteristics of this cell (fig 4).

The Naegeli type of monocytic leukemia has the myeloblast or stem cell as the parent cell and it has been regarded by some investigators as a form of myelogenous leukemia, because of its tendency to terminate

4 Giffin, H. Z., and Watkins, C. H. The Distinction Between Splenic Anemia and Subleukemic Splenic Reticulo-Endotheliosis, *Am J M Sc* **188** 761-767 (Dec) 1934.

in that condition. One of us (C H W)⁵ had under observation a patient with chronic myelogenous leukemia who, during the last seven months of illness, presented all the features of typical monocytic leukemia of the myeloblastic type. The diagnosis rests on the morphologic characteristic of the parent cell, which in this case is the myeloblast. The myeloblast is a relatively large cell, with the nucleus containing a delicate sievelike arrangement of chromatin. The chromatin is usually granular, but it may be in thin strands and is sharply differentiated from the parachromatin, which stains a faint pink with Wright's stain. The chromatin is usually in the background, so that the parachromatin stands out more clearly and seems to predominate, giving the appearance of a sieve, the so-called sievelike nuclear pattern so characteristic of the myeloblast. Usually several nucleoli are present. The nuclear membrane is delicate but nevertheless distinct. The cytoplasm is usually bluish and may have a moderately mottled appearance, but this is of little importance in distinguishing the cell. During differentiation the nucleoli disappear, the chromatin of the nucleus becomes more prominent and the strands thicken and show a tendency to form the stringlike clumps that are typical of the mature monocyte. The cytoplasm gradually loses the bluish tint and becomes slate gray, which is one of the distinguishing features of the mature monocyte.

The diagnosis of the type of monocytic leukemia is made by the presence in the peripheral blood of the myeloblast and the intermediate forms between it and the mature monocyte. In an occasional case there may be immaturity of other myeloid leukocytes, with only a slight predominance in monocytes. For this reason it is probable that the Naegeli type of monocytic leukemia is a form of myelogenous leukemia and not a distinct entity. As long as there is so little knowledge regarding the physiology of the hematopoietic system and the ultimate function of the monocyte, there will continue to be confusion of the subject, and numerous classifications will be proposed. However, at least for the present, it seems that a diagnosis of a separate entity of monocytic leukemia of the Naegeli type is justified, particularly when the monocyte predominates in the peripheral blood to the practical exclusion of the other myeloid leukocytes.

Monocytic leukemia with the reticular cell (reticulo-endothelial cell) as the parent cell, the so-called monocytic leukemia of Schilling, is morphologically, at least, a distinct entity and may be readily differentiated from the Naegeli type of monocytic leukemia by the predominance during the developmental or differentiative phase of the features of the reticulo-endothelial cell, which are even carried over to a certain extent in the mature monocyte. The free reticular cell is, from the

5 Watkins, C H. Unpublished observations.

morphologic standpoint, a distinct cell type. It generally is larger than the ordinary leukocyte and usually has an eccentric nucleus, which may be slightly elongated but which usually is almost spherical and presents an arrangement of chromatin that suggests that a groove runs through the central portion of the nucleus. When Wright's stain has been used the chromatin is blue, is sharply differentiated from the parachromatin and is arranged in fine granular strands. The nuclear membrane is sharply defined and delicate, the whole nucleus has a clean-cut appearance. The cytoplasm, on the other hand, is generally abundant and rather grayish blue, with a blotchy appearance. Cytoplasmic protrusions are relatively common, and in certain instances the cytoplasmic portion of the cell may stain poorly. The entire cell has a distinctly delicate and youthful appearance. One or more nucleoli may be present in the nucleus. In comparing this cell with the ordinary myeloblast one notes the marked morphologic differences, as illustrated in figure 4. During the differentiative phase to the mature form of monocyte the nuclear pattern becomes heavier and the chromatin strands thicker, but the tendency to groove seems to remain even into the mature form. The cytoplasmic changes are not marked. There is a tendency for a slate color to predominate, and there may be a blotchy appearance in the cytoplasmic changes, which is apparently produced by differences in staining quality.

REVIEW OF THE LITERATURE

The cutaneous manifestations of various types of monocytic leukemia have been described recently in articles by Mercer,⁶ Loveman,⁷ Lynch⁸ and Wayson and Weidman.⁹ Specific involvement of the skin frequently begins by simulating the picture of mycosis fungoides, and necrotic, purpuric and hemorrhagic lesions frequently are encountered. Generalized pustular and even bullous lesions, similar to those seen in the other lymphoblastomas, have been described.¹⁰ An increase in the

6 Mercer, S. T. The Dermatoses of Monocytic Leukemia, *Arch Dermat & Syph* **31** 615-635 (May) 1935.

7 Loveman, A. B. Monocytic Leukemia Cutis. Report of a Case with Biopsy Studies, *South M J* **29** 357-363 (April) 1936.

8 Lynch, F. W. Cutaneous Lesions Associated with Monocytic Leukemia and Reticulo-Endotheliosis, *Arch Dermat & Syph* **34** 775-796 (Nov.) 1936.

9 (a) Wayson, J. T., and Weidman, F. D. Aleukemic Reticulosis. An Additional Member of the So-Called Cutaneous Lymphoblastomas, *Arch Dermat & Syph* **34** 755-774 (Nov.) 1936. (b) Weidman, F. D., and Custer, R. P. The Scope of the So-Called "Cutaneous Lymphoblastomas" in Relation to Lesions of the Haematopoietic System, in *Deliberationes Congressus Dermatologorum Internationalis*, IX, Budapest, L. Nekam, 1935, vol. 2.

10 Goeckerman and Montgomery.¹ Barney.² Lynch.⁸

number of monocytes is frequently seen in a Kaposi sarcoma,¹⁰ which may at times be associated with the lymphoblastomas.¹¹ The inter-relationship between the various types of lymphoblastoma has been emphasized by many authors,¹² and Fraser and Schwartz¹³ have noted especially the prominent rôle that the reticulo-endothelial system of the skin plays in the various lymphoblastomas.

COMMENT

Our cases illustrate most of the various cutaneous manifestations of monocytic leukemia. Case 1, of the Naegeli type, was significant in that the patient was under observation and thorough studies of the blood were made over a period of four years. The condition at first had the clinical features of mycosis fungoides and then of a fairly generalized erythroderma, and later somewhat necrotic nodules developed, yet until the terminal stages of the disease the process apparently remained confined to the skin. There were no changes in the blood or any involvement of the internal organs until shortly before death. Biopsy of the skin was at no time diagnostic as to the type of lymphoblastoma but consistently showed activity of the reticulo-endothelial system, including an increase in *Gitterfasern* and in mature monocytes. It is unfortunate that no microscopic examination of a cutaneous lesion was made just before death or post mortem, as a more specific histopathologic picture might have been encountered. This case represents, we believe, an example of the autochthonous cutaneous origin of monocytic leukemia of the Naegeli type.

Case 3, in contrast, is an example of the Schilling type of monocytic leukemia of autochthonous origin. Beginning with cutaneous lesions resembling mycosis fungoides, as in Weidman's⁹ case, the condition later resolved into an exfoliative dermatitis. A peculiar type of grooved and serrated immature monocytic cell could be definitely recognized, both in the second biopsy specimen of the skin and in later blood smears, in retrospect, a few grooved cells were observed in the first specimen of skin taken for biopsy a year previously. This, we believe, is the first case of exfoliative dermatitis to be reported as due to monocytic leuke-

10a Dorffel, Julius. Histogenesis of Multiple Idiopathic Hemorrhagic Sarcoma of Kaposi, *Arch Dermat & Syph* **26** 608-634 (Oct) 1932.

11 Lane, C G, and Greenwood, A M. Lymphoblastoma (Mycosis Fungoides) and Hemorrhagic Sarcoma of Kaposi in the Same Person, *Arch Dermat & Syph* **27** 643-657 (April) 1933.

12 Loveman, A B. Cutaneous Manifestations of the Lymphoblastomas. Report of a Case of Hodgkin's Disease, *J A M A* **104** 1583-1586 (May 4) 1935. Wayson and Weidman^{9a} Goeckerman and Montgomery¹

13 Fraser, J F, and Schwartz, H J. Neoplastic Disease of the Reticulo-Endothelial System, *Arch Dermat & Syph* **33** 1-10 (Jan) 1936.

mia (Schilling) In both cases 1 and 3 the early histopathologic picture of the skin closely resembled that of mycosis fungoides We are familiar with the increase in *Gitterfasern* and the increase in monocytes in mycosis fungoides¹³ This condition may persist as such or terminate as lymphosarcoma, especially of the reticulum cell type, or it may even terminate as any of the other lymphoblastomas It is not surprising, therefore, to find the Naegeli and Schilling types of monocytic leukemia falling into this group In case 4 the cutaneous changes were recognized first, and negative results of biopsy of a lymph node speak against the systemic origin of the condition A hemocytologic picture of lymphatic leukemia was encountered at the time biopsy of the skin showed lymphoblastoma and suggested the presence of Hodgkin's disease Later, both biopsy and the hemocytologic picture revealed monocytic leukemia (Schilling), when an exfoliative dermatitis was present clinically Recent blood smears showed more the picture of lymphatic leukemia This case again emphasizes the interrelationship of the lymphoblastomas

Case 2 was a case of typical monocytic leukemia of the Naegeli type in which, in the terminal phase, discrete specific nodules were present in the skin, such as are frequently noted in leukemia cutis, especially of the lymphatic type, and rarely in myelogenous leukemia There was nothing characteristic in the clinical appearance of these nodules

Case 5 revealed generalized and the most severe purpuric and hemorrhagic lesions we have ever seen and justly emphasizes, as has been brought out by Lynch⁸ especially, that purpuric lesions are often encountered in monocytic leukemia of the Schilling type A few such lesions were present in case 4 Purpuric and necrotic cutaneous lesions are not an uncommon finding in any of the lymphoblastomas, especially in the terminal phases of the disease Unfortunately, no specimen for biopsy was taken in case 5 so we do not know whether the cutaneous lesions were simply toxic or represented true specific infiltration of the skin

TREATMENT

It has been the experience of one of us (C H W) that monocytic leukemia of the Schilling type is a more benign form than the Naegeli type, although of course it eventually proves fatal It seems that high voltage roentgen or radium therapy is indicated if the process is not too acute but the dose should be given with careful observation of the hematologic changes, in order to determine the resistance of the cells to treatment The cutaneous lesions frequently show a striking though temporary involution after superficial local roentgen therapy, although involution of all lesions also may result after systemic high voltage roentgen therapy, including lesions in areas of the skin not

treated. Local applications, in an attempt to control the pruritus or secondary infection, and arsenic and fever therapy also may be of temporary value.

SUMMARY AND CONCLUSIONS

Distinction is made between monocytic leukemia of the Naegeli and that of the Schilling type on the basis of the hemocytologic pictures. Either type may be of primary autochthonous cutaneous origin. The type of cutaneous manifestations of either condition may be specific or nonspecific and may vary from discrete necrotic nodules or purpuric lesions to generalized exfoliative dermatitis. A distinctive histopathologic picture of monocytic leukemia of the Schilling type may be observed on examination of the skin, corresponding to the hemocytologic picture. Occasionally, myelogenous leukemia may terminate as monocytic leukemia of the Naegeli type,⁵ or, as in case 4, lymphatic leukemia may result in monocytic leukemia (Schilling) and still later again present the blood pictures of both conditions. Monocytic leukemia of the Schilling type (leukemic reticulo-endotheliosis) may assume an acute or chronic form, and even aleukemic reticulosis may be encountered.⁹¹

It is important, therefore, to correlate the cutaneous as well as the general clinical, pathologic and hemocytologic observations in a given case in order to arrive at a correct diagnosis. A prolonged period of observation may be necessary before it is possible to ascertain the type of lymphoblastoma that will eventuate.

ALTERATIONS IN SERUM PROTEIN AS AN INDEX OF HEPATIC FAILURE

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For some time we have been interested in the changes in the protein content of the serum in hepatic disease. The basis of this interest lies in numerous clinical and experimental observations. Whipple¹ found that the liver produces fibrinogen. Less conclusively other experiments have indicated that the liver is the site of formation of the albumin of serum. Clinical observations and studies show that there are changes in the protein content of the blood in hepatic disease. This fact was first observed by Grenet² and Gilbert³ in 1907, who found a diminution of the total protein content of the blood in cases of cirrhosis of the liver. Filinski⁴ described cases of cirrhosis in which the total protein content was decreased, chiefly in the albumin fraction, with some elevation of the globulin content. His observation, confirmed by Abrami and Wallich,⁵ have received repeated verification in the literature recently reviewed by Myers and Keefer⁶ and Snell.⁷ Serum protein

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1 Whipple, G H. Fibrinogen. An Investigation Concerning Its Origin and Distribution in the Body, *Am J Physiol* **33** 50 (Jan) 1914

2 Grenet, H. Diminution des albumines du serum sanguin chez les hepatiques, *Compt rend Soc de biol* **63** 552, 1907

3 Gilbert, A, and Chiray, M. Diminution des substances albumineuses du serum sanguin chez les cirrhotiques ascitiques, *Compt rend Soc de biol* **63** 487, 1907

4 Filinski, W. L'augmentation de taux de la globuline dans le serum du sang, *Presse med* **20** 236 (March 18) 1922

5 Abrami, P, and Wallich, R. Modifications du serum sanguin au cours des cirrhoses du foie avec ascites. Inversion du rapport serums-globulines, *Compt rend Soc de biol* **101** 291 (May 31) 1929

6 Myers, W K, and Keefer, C S. Relation of Plasma Proteins to Ascites and Edema in Cirrhosis of the Liver, *Arch Int Med* **55** 349 (March) 1935

7 Snell, A M. Changes in Proteins of Blood in Hepatic Disease, *Proc Staff Meet, Mayo Clin* **10** 489 (July 31) 1935

has been studied in forms of hepatic damage other than cirrhosis and has been found to be altered roughly in proportion to the severity of the damage (Myers and Keefer⁶)

Experimentally there have been extensive studies of the blood protein in animals under various conditions affecting the liver, particularly necrosis after the administration of chloroform and phosphorus and after ligation of the common duct, the production of an Eck fistula and hepatectomy. Beginning with the studies of Kerr, Hurwitz and Whipple,⁸ experimental attempts have been made to determine the rôle of the liver in protein metabolism. Whipple and his associates showed that depletion of the protein content of the serum by plasmapheresis is followed by a regeneration of the protein and that globulin is replaced more rapidly than albumin. The regeneration of the protein was delayed in animals in which the liver was damaged by phosphorus or chloroform before depletion of the plasma. These workers attributed part of the slow regeneration of protein to the low intake of food associated with hepatic injury and consequent intoxication. Henriques and Klausen⁹ recorded a decrease in the albumin but not in the globulin content of the plasma in rabbits after phosphorus poisoning. Sawada¹⁰ found a decrease in the albumin content and a slight elevation of the globulin content in animals with hepatic damage from phosphorus, chloroform and tetrachloride poisoning and also from inoculation with *Schistosomum japonicum*.

In the hepatic damage following ligation of the common bile duct Henriques and Klausen,⁹ Sawada,¹⁰ Bollman¹¹ and Foley and his associates¹² found a decrease of the albumin content with an increase of globulin occurring from one to three months after the ligation. Pertinent is the criticism of Whipple and his associates⁸ that under the influence of obstructive jaundice there is a marked disinclination on the part of the animal to eat, and because of this, the inadequate supply

8 Kerr, W. J., Hurwitz, S. H., and Whipple, G. H. Regeneration of Blood Serum Proteins. I. Influence of Fasting upon Curve of Protein Regeneration Following Plasma Depletion, *Am J Physiol* **47** 356, 1918, II. Influence of Diet upon Curve of Protein Regeneration Following Plasma Depletion, *ibid* **47** 370, 1918, III. Liver Injury Alone. Liver Injury and Plasma Depletion, the Eck Fistula Combined with Plasma Depletion, *ibid* **47** 379, 1918.

9 Henriques, V., and Klausen, U. Untersuchungen über den Serumalbumin- und Serumglobulingehalt des Serums unter wechselnden Umständen, *Biochem Ztschr* **254** 414, 1932.

10 Sawada, T. Biochemical Investigation of the Blood in Cases of Experimental Disturbance of Liver Function, *Jap J Gastroenterol* **3** 38, 1931.

11 Bollman, J. L. Influence of Diet in the Experimental Production of Ascites, *Proc Staff Meet, Mayo Clin* **3** 137, 1928.

12 Foley, E. F., Keeton, R. W., Kendrick, A., and Darling, D. Serum Protein Studies Following Ligation of the Common Bile Duct, to be published.

of protein contributes to the low values for albumin. Diet was not mentioned by Henriques and Klausen or by Sawada. In the studies quoted by Bollman¹³ milk, a complete protein, was the chief constituent of the diet. Foley and his colleagues¹² found that control animals, which had not been operated on and which were fed the same diet as the dogs that had been operated on (milk, cream, eggs, butter, cheese and bread), did not show alterations in the protein content of the serum. Dogs with Eck fistulas (Whipple⁸) show a distinct inability to regenerate the protein of the blood after depletion of the plasma. Jurgens and Gebhardt,¹⁴ working with dogs with Eck fistulas, found that an increase in globulin developed two or three weeks after the operation. Meat feeding depressed the albumin value and raised the globulin value while carbohydrate feeding reversed this phenomenon in the normal direction. In hepatectomized animals Mann and Magath¹⁵ found a decrease in the total protein content and a decrease in the albumin and globulin values, with a tendency for the reversal of the albumin-globulin ratio. Similar results were obtained by Cantô¹⁶. By diet alone Holman, Mahoney and Whipple¹⁷ were able to produce alterations in the protein similar to those which have previously been mentioned as being associated with disorders of the liver. This diet, however, contained no animal and a minimal amount of vegetable protein. On this diet low in protein some dogs maintained a normal value for protein for seven weeks, while others showed a reversal of the albumin-globulin ratio after two months. Weech, Snelling and Goettsch¹⁸ described a diet supplying an inadequate intake of protein on which dogs showed a progressive decrease of the protein (albumin) content of the serum and a constant level for globulin, with the subsequent development of edema and ascites. In approximately twenty experiments the decrease in the total protein (albumin) content of the serum was 1 Gm per hundred cubic centi-

13 Bollman, J. L., Mann, F. C., and Magath, T. B. Studies of the Physiology of the Liver, *Am J Physiol* **78** 258, 1926

14 Jurgens, R., and Gebhardt, F. Ueber die Eiweisskörper des Blutes bei experimenteller Leberschädigung durch die Eck-Fistel, *Arch f exper Path u Pharmakol* **174** 532, 1934

15 Mann, F. C., and Magath, T. B. Die Wirkungen der totalen Leberexstirpation, *Ergebn d Physiol* **23** 212, 1924

16 Cantô, A. Variations des proteines du plasma sanguin apres l'hepatectomie, *Compt rend Soc de biol* **104** 1103, 1930

17 Holman, R. L., Mahoney, E. B., and Whipple, G. H. Blood Plasma Protein Controlled by Diet. I. Liver and Casein as Potent Diet Factors, *J Exper Med* **59** 251 (March) 1934

18 Weech, A. A., Snelling, C. E., and Goettsch, E. The Relation Between Plasma Protein Content, Plasma Specific Gravity and Edema in Dogs Maintained on a Protein Inadequate Diet and in Dogs Rendered Edematous by Plasmapheresis, *J Clin Investigation* **12** 217, 1933

eters The evidence may be summarized in the quotation of Keri, Hurwitz and Whipple ⁸ "All this experimental evidence points to the liver as concerned in maintaining the normal level of the serum proteins"

Since alterations of the protein may occur in the presence of hepatic disease, we wished to determine the diagnostic and prognostic value of such alterations A study of patients with cirrhosis of the liver, compensated and decompensated, and others with intrahepatic and extrahepatic jaundice was made The control groups included patients with ascites without clinical cirrhosis and patients on severely deficient diets in whom there was no evidence of hepatic disease These groups were sufficiently diversified to permit a study of chronic, advanced, diffuse hepatic damage as well as varying degrees of less extensive damage We were able to observe to some extent the relation of the intake of food to the alteration of the protein content of the serum

METHODS

About 15 cc of blood was drawn from the cubital vein while the patient was in a fasting state After clotting had occurred the serum was drawn off with a pipet Quantitative determinations of the protein were made according to the gasometric method of Van Slyke ¹⁹ For a group of healthy males and females our results compare favorably with the normal values given by Peters and Van Slyke ²⁰

RESULTS

A Cirrhosis of the Liver with Ascites—There were twenty-one patients with cirrhosis of the liver with ascites (table 1), seventeen of whom presented the classic picture of advanced portal cirrhosis with marked ascites There were two patients with cardiac cirrhosis in whom evidences of hepatic damage persisted after cardiac compensation had been established With the exception of three patients, none showed albumin in the urine In two of these the quantity was insignificant In no instance was paracentesis performed before the protein of the serum was measured This precluded the loss of proteins by mechanical removal The results are practically identical with those obtained by Filinski ⁴ and others, in that a decrease in the albumin content and an elevation of the globulin content with a reversal of the albumin-globulin ratio were noted In four instances the total protein content was normal, but in these the high values for total protein were due to an increase in the globulin content (5 Gm or more per hundred cubic centimeters)

19 Peters, J, and Van Slyke, D Quantitative Clinical Chemistry Methods, Baltimore, Williams & Wilkins Company, 1932

20 Peters, J, and Van Slyke, D Quantitative Clinical Chemistry Interpretations, Baltimore Williams & Wilkins Company, 1932

TABLE 1—*Cirrhosis with Ascites*

Patient		Protein, Gm per 100 Cc				Blood				Albumin in Urine	Dye Test*	Size of Spleen	Survival After Determination, Days	Type of Cirrhosis		
		Total	Albumin	Globulin	Ratio	Albumin Globulin Ratio	Non protein Nitrogen, Mg per 100 Cc	Hemo globin, Gm per 100 Cc	Red Blood Cells, Millions Cu Mm					Icteric Index	Clinical Diagnosis	Postmortem Diagnosis
No	Name															
1	J M	7.84	2.38	5.46	0.40	30.0	10.0	3.98	125	+	—	+	5		Atrophic acute yellow necrosis	
2	J W	7.56	1.86	5.70	0.32	26.4	11.0	4.36	40	0	60	+	13	Atrophic	Atrophic	
3	S K	6.10	2.42	3.68	0.65	23.2	7.0	2.70	15	0	—	+	14	Atrophic	Atrophic	
4	J B	5.42	1.53	3.89	0.37	31.0	8.8	2.80	30	0	40	+	15	Atrophic	Atrophic	
5	F B	4.89	1.64	3.25	0.50	32.3	9.8	3.10	22	0	—	+	18	Atrophic	Atrophic	
6	W M	5.98	2.18	3.80	0.77	17.0	8.0	3.20	75	0	40	+	21		Atrophic	
7	M N	5.96	1.77	4.19	0.42	26.0	10.0	3.20	28	0	—	+	27	Atrophic	Atrophic	
8	C D	6.95	1.95	5.00	0.39	24.3	10.0	3.09	18	Trace	45	+	31		Atrophic	
9	C H	6.29	1.38	4.91	0.29	21.5	10.0	3.40	18	0	—	+	36		Atrophic	
10	J Z	5.34	2.42	2.92	0.89	43.0	11.0	3.80	12	0	30	+	43		Atrophic	
11	J S	5.47	2.04	3.43	0.59	42.3	8.0	3.48	14	0	35	+	49		Atrophic	
12	J K	7.90	2.36	5.54	0.40	24.0	9.0	2.20	17	0	40	+	56	Atrophic	Atrophic	
13	M G	6.06	2.30	3.76	0.61	24.0	7.0	2.60	25	0	25	+	60		Atrophic	
14	J K	4.14	1.83	2.31	0.79	19.2	8.0	2.60	22	0	50	+	70	Alcoholic	Alcoholic	
15	J H	6.11	3.08	3.06	1.00	26.2	14.0	4.60	8	0	20	+	75	Alcoholic	Alcoholic	
16	S	7.87	1.75	6.12	0.28	41.0	15.0	4.27	12	0	30	0	77	Alcoholic	Alcoholic	
17	P B	6.38	1.27	5.11	0.25	26.8	10.0	3.15	12	0	40	+			Amyloid	
18	M N	6.91	3.02	3.89	0.76	19.6	9.6	3.10	102	+	50	0		Alcoholic	Obstructive biliary	
19	L B	6.71	2.97	3.74	0.80	28.6	9.0	3.52	72	0	60	+		Obstructive biliary	Obstructive biliary	
20	D K	5.63	2.57	3.06	0.84	42.0	16.0	4.47	11	++	20	+	—	Cardiac	Cardiac	
21	J M	4.70	2.07	2.63	0.79	23.7	13.2	4.40	14	0	—	+	—	Cardiac	Cardiac	

* Percentage of bromsulphalein retained at the end of thirty minutes

TABLE 2—*Decompensated Cirrhosis with Subsequent Compensation*

	Blood											Size of Spleen	Comments	
	Protein, Gm per 100 Cc				Nonprotein Nitrogen, Mg per 100 Cc			Red Blood Cells, Millions		Icteric Index	Albu min in Urine			Dye Test
	Total Protein	Albumin	Globulin	Ratio	Albumin Globulin Ratio	Hemo globin, Gm per 100 Cc	Cu	Mm						
12/ 3/34	6 60	1 86	4 74	0 40	21 98	4 7	2 85	42	0	35	+	Ascites present, 500 cc of blood given 12/10 and 12/17		
12/18/34	6 78	3 27	3 51	0 90	18 97	8 7	3 50	24	0	—	+	500 cc of blood given 12/28		
1/ 2/35	7 28	3 44	3 84	0 89	23 10	8 5	3 70	14	0	—	+	500 cc of blood given 1/9/35, no ascites		
6/16/35	7 57	4 31	3 26	1 30	22 80	11 5	4 20	12	0	15	+	No ascites		
1/18/36	7 94	4 87	3 07	1 60		12 0	4 50	12		—	+	No ascites liver greatly enlarged		

The data are arranged in the order of duration of life (expressed in days) after the determinations were made. The seventeen patients with portal cirrhosis showed an average duration of life of forty-four days, with a minimum of five and a maximum of seventy-seven days. These results merely affirm the clinically recognized fact that ascites (a symptom indicating portal decompensation) in cirrhosis is an unfavorable prognostic sign. It is suggested that these striking changes in the protein of the blood represent a failure of the proteogenic function of the liver and therefore a serious impairment of a vital metabolic process.

The Decrease in Albumin Is Not Due to Mechanical Removal In table 2 are presented the results obtained for a patient with the hypertrophic form of alcoholic cirrhosis during decompensation and subsequent compensation. A year previously this patient had been in the hospital with jaundice and ascites which had developed after a period of alcoholic excesses. These symptoms disappeared after the patient had spent two months in the hospital, but at the time of his discharge the spleen and liver were markedly enlarged. In December 1934 he returned to the hospital with jaundice and ascites, which again had developed after an alcoholic episode. During the period of portal decompensation the usual changes in the protein occurring in hepatic failure were observed. Four transfusions of whole blood were given at weekly intervals, in addition to large amounts of carbohydrate. After the second transfusion the value for albumin practically doubled. Improvement continued, with the complete disappearance of both jaundice and ascites after the fourth transfusion. After compensation the protein assumed a normal direction but not a normal level. Determinations made six months and one year later showed a high level for globulin but a practically normal level for albumin. It seems that during the acute exacerbation of the hepatic disturbance this patient was unable to maintain his stores of protein, but he has since been able to supply adequate quantities of protein after its restoration through blood transfusion and reabsorption of the ascitic fluid.

In table 3 are listed the data for patients with ascites without clinical cirrhosis of the liver. In this group were five patients with ascites due to carcinoma, with metastasis either to the liver or to the peritoneum. Paracentesis had been performed twice on one patient prior to his admission to the hospital but not on the others. Although the loss of protein in the ascitic fluid is comparable to that which occurs in cirrhosis prior to paracentesis, similar changes did not occur in the protein of the serum. Likewise in the patients with ascites due to tuberculous peritonitis and congestive heart failure, the protein of the serum behaved in a normal manner. These instances indicate that there may be a transudation of protein into larger accumulations of ascitic fluids with-

TABLE 3—*Ascites Without Clinical Cirrhosis of the Liver*

Patient No	Name	Blood						Albumin in Urine	Dye Test	Size of Spleen	Diagnosis			
		Protein, Gm per 100 Cc			Non protein Nitrogen, Mg per 100 Cc	Hemo- globin, Gm per 100 Cc	Red Blood Cells, Millions Cu Mm				Icteric Index	Autopsy	Clinical	
		Total	Albumin	Globulin										
1	A R	7.29	3.99	3.30	1.20	30.0	9.5	4.00	9	0	—	0	Carcinoma of tail of pancreas, metastases to liver	
2	J O	6.63	3.31	3.14	1.10	46.0	11.0	4.20	21	0	10	0	Myxoma peritonei	Myomatous carcinoma of appendix with metastases to peritoneum
3	E M	7.02	3.50	3.52	1.00	30.0	13.0	4.40	7	0	10	0	Carcinoma of peritoneum, nutmeg liver	
4	C S	5.12	3.07	2.05	1.50	61.0	8.4	2.75	39	0	10	0	Carcinoma of stomach, metastases to liver	
5	J C	7.53	4.52	3.01	1.50	30.0	9.9	4.95	160	0	100	0		Carcinoma of extra hepatic bile passages
6	A R	7.63	4.23	3.40	1.19	30.3	10.0	4.11	8	0	—	0		Tuberculous peritonitis
7	M M	6.53	4.40	2.13	2.60	34.9	12.0	4.85	10	0	—	0		Congestive heart failure
8	F H	5.28	3.47	1.81	1.90	26.0	11.0	4.40	11	Trace	10	0		Congestive heart failure

out alterations of the serum protein. As was mentioned previously, in our patients with cirrhosis paracentesis had not been performed prior to the determinations of the protein, so that the amount of protein lost was represented by that quantity which had passed into the accumulated ascitic fluid. By contrast, the results obtained in another case (table 3, patient 2) are especially important. Clinically this patient presented marked ascites, for the relief of which paracentesis was frequently performed. Over a period of one hundred and eighty days there was removed from the abdomen approximately 59,200 cc of a thick, mucilaginous fluid, analysis of which yielded 5.47 Gm of total protein per hundred cubic centimeters of fluid (albumin, 2.16 Gm, globulin, 3.31 Gm). During this time the total estimated loss of protein, exclusive of the initial amount, was 2,445 Gm, or a daily loss of 13.5 Gm. The protein content of this fluid was practically the same as that of blood, so that at each paracentesis the experimental conditions of plasmapheresis were duplicated. The determinations on the blood made at the time of the final paracentesis (total protein, 6.97 Gm, albumin, 3.43 Gm, globulin, 3.54 Gm) showed a negligible fall in the amount of protein as compared with the quantity present in the serum (total protein, 6.65 Gm, albumin, 3.51 Gm, globulin, 3.14 Gm) six weeks prior to the initial tapping. At autopsy the liver grossly was normal in size and appearance, but the visceral and the parietal peritoneum were studded with biscuit-sized carcinomatous nodules which had their origin in a myxomatous carcinoma of the appendix. This patient then represents an instance of the extreme loss of protein into the ascitic fluid in the presence of a normal liver. In spite of the repeated removal of fluid, there was no depletion of the serum albumin, such as occurred in the patients with cirrhosis of the liver from whom the ascitic fluid had not been removed. This case corroborates the experience of others in demonstrating that the loss of protein into the ascitic fluid is per se not the cause of the depletion of the serum albumin. This question of the loss of albumin in the ascitic fluid and its relation to hypo-albuminemia has recently been discussed by Myers and Keefer⁶. They cited cases of cirrhosis in which repeated paracentesis, with the loss of as much as 18 Gm of protein per day in the ascitic fluid, did not lead to a progressive decline in the level of the blood protein. They pointed out that this amount of protein lost daily can be regenerated in experimental animals undergoing plasmapheresis. They concluded that loss of the protein in the ascitic fluid is not adequate explanation of the low levels of protein in the blood.

The Decrease in Albumin Is Not Due to an Inadequate Intake of Protein. Five patients were studied who showed no clinical evidences of hepatic damage, but there were marked dietary restrictions. The first

patient was a young woman who, because of a psychasthenic reaction, voluntarily reduced her intake of food so that she lost 16 pounds (7 Kg) her weight being reduced from 118 to 72 pounds (53.5 to 33 Kg) in from twelve to fourteen weeks. The emaciation was extreme, and polyneuritis was so severe that she could only shrug her shoulders. She had to be turned in bed by nurses and fed for ten days with a nasal catheter. The second case was that of a woman with chronic intestinal obstruction. There was protracted vomiting for eight weeks, little food being retained, except for brief intervals during which liquids were administered through a duodenal tube. Water and salt were given parenterally. The third case was that of a man who had been living on scraps of food salvaged from garbage cans. He was found in an exhausted state on the street and showed severe scurvy with extensive hemorrhages and marked anemia. While his intake of protein was not known, it was deficient. There were two patients with malignant growths, one having sarcoma of the bone and the other having carcinoma of the lung. Both patients showed marked anorexia and emaciation. In all these cases²¹ there was some decrease in the total protein content of the serum but no elevation of the globulin content. The albumin-globulin ratio remained normal. It has frequently been pointed out that globulin is regenerated more readily than albumin. Although exact quantitative estimations of the intake of food of the patients with cirrhosis are not given, it is known that they (table 1) ate ward diet satisfactorily and hence must have obtained more protein than the control patients mentioned previously. In this connection the metabolic experiments of Liu and his colleagues²² are important. Their studies of human beings in whom nutritional edema had developed as the result of starvation indicated the presence of a depletion of the protein of the plasma, with a reversal of the albumin-globulin ratio. The addition of 28 Gm of protein to the daily ration reestablished the normal level of the protein. From this experience it seems that a small intake of protein is adequate to prevent the fall of the protein content of the plasma when there is no deficiency in synthesis. In nephrosis there is no evidence of alteration of hepatic function or of its capacity to regenerate protein. In this condition it has been shown by Barker and Kirk²³ that the daily loss of protein in the urine is from 5 to 60 Gm and that a loss of 4 Gm a day is associated with a fall in the protein level of the serum. This drop is attributed to the loss in the urine. The loss affects chiefly the

21 The tabulated detailed data for these patients are omitted to conserve space.

22 Liu, S. H., Chu, H. I., Wang, S. H., and Chung, H. L. Nutritional Edema. *Chinese J. Physiol.* 6: 73, 1932.

23 Barker, M. H., and Kirk, E. J. Experimental Edema (Nephrosis) in Dogs in Relation to Edema of Renal Origin in Patients, *Arch. Int. Med.* 45: 319 (March) 1930.

albumin factor and progresses to a reversal of the albumin-globulin ratio. They further stated that patients losing less than 10 Gm of albumin per day show a "remarkable benefit from a high protein diet," which restores the protein of the serum. In the presence of diffuse hepatic damage an adequate or high protein diet does not maintain or reestablish the protein content of the blood, because of the impairment of the proteogenic function. Further evidence that the change in the protein is not the result of protein deprivation is illustrated by patient 1 (table 1). This middle-aged man had an adequate intake of food until the onset of hepatic necrosis. One week before entrance to the hospital he had taken some unknown drug to induce sleep. On entrance marked jaundice and some ascites were noted. Determinations of the protein content of the serum were made on his second day in the hospital, or eight days after the onset of illness. Although he was able to partake of the ward diet, which contained 60 Gm of protein daily, the albumin content had dropped to 2.36 Gm, and the globulin content had risen to 5.46 Gm. There followed progressive jaundice, cholemia, hemorrhagic diathesis and death five days later. Autopsy revealed a small liver with extensive necrosis of the parenchyma. The history, obtained from the patient's wife, did not indicate dietary restriction prior to his entrance. Similar alterations of the protein content of the serum were recorded by Longcope²⁴ in acute yellow atrophy of the liver.

The Decrease in Albumin in Patients with Hepatic Damage Persists in Spite of an Increased Intake of Protein. The history of patient 9 (table 1) is significant. This patient had typical cirrhosis of the liver with marked ascites. He consumed at our suggestion 120 Gm of liver daily, because the experiments of Holman, Mahoney and Whipple¹⁷ showed the efficiency of liver in regeneration of plasma protein after plasmapheresis. The clinical progress of the disease seemed to be more rapidly downward than usual. At the time of the first determination of the protein content of the serum he was an ambulatory outpatient, yet the progress of his illness was such that death occurred thirty-six days later. One wonders whether the rapid deterioration could not be ascribed to the liver diet. This would be in keeping with the results of Bollman,¹¹ who noted that the addition of meat to the diet of dogs with ligated common ducts regularly produced ascites and symptoms similar to "meat intoxication" occurring in dogs with Eck fistulas. A similar study was made of another patient with cirrhosis of the liver on a liver diet, but records of the protein content of the blood are not available. Such data indicate that in cirrhosis the addition to the diet of adequate protein ("building stones") may not favorably influence

24 Longcope, W. T. The Importance of Disturbances in Nutrition in Edematous States, *New England J. Med.* **210** 1243, 1934.

the regeneration of protein. They suggest also that the damaged liver not only loses its capacity to synthesize serum protein but may lose also its ability to protect the body from toxic effects of ingested proteins.

B Other Forms of Hepatic Damage—In cases of hepatic disease manifested by jaundice without ascites (table 4) there may be either extrahepatic obstruction or intrahepatic destruction. There were eleven patients with extrahepatic obstruction for whom the diagnosis was established by operation or autopsy. Among these were three patients with stone in the common duct (patients 1 to 3) with marked reversal of the albumin-globulin ratio. All three died in spite of adequate preoperative management, conservative surgical measures and careful postoperative care, including transfusions, infusions of dextrose and buffer solution, duodenal siphonage and the administration of decholin. In contrast, two patients with calculous cholecystitis (patients 4 and 5) with normal values for protein made an uneventful postoperative recovery. In five patients with malignant extrahepatic obstruction with jaundice, less marked alteration of the protein occurred. In the group of patients with intrahepatic jaundice the results of the studies of the serum protein paralleled the clinical course. Three patients with pneumonia (patients 12 to 14) showed a reversal and death. Two of these were jaundiced. One other patient with pneumonia (not jaundiced) showed no reversal and recovered. Five patients with "catarrhal jaundice" (patients 16 to 20) showed no reversal and the usual recovery. One patient with chronic low grade jaundice,²² a young woman whose employment required the use of benzene showed no reversal. This patient's clinical condition remained unchanged after one year of observation. There was one young alcoholic patient with delirium tremens and jaundice²³ who had complete recovery. There was no reversal, even though there had been dietary restriction.

C Application of This Principle in Diagnosis of Hepatosplenomegaly—There were four patients with hepatosplenomegaly for whom studies of the protein content of the serum were of diagnostic value.²¹ In one of these, while the total protein content was close to the level for edema, there was no alteration of the globulin content. A diagnosis of cirrhosis of the liver was eliminated on this basis. Autopsy revealed Hodgkin's disease. In one of the others there was an elevated globulin content with a slight decrease in the albumin content and a reversal of the ratio. This patient had a clinical history of untreated syphilis, with positive serologic tests. Elevation of the globulin content of the serum has been observed in syphilis by Noguchi.²⁵ Hence a diagnosis of syphilis of the liver which had not reached the stage of decompensated cirrhosis

²⁵ Noguchi, H. The Relation of Protein Lipoids and Salts to the Wassermann Reaction, *J. Exper. Med.* **11** 84, 1909.

TABLE 4—Other Forms of Hepatic Damage Without Ascites

Patient		Blood										Diagnosis				
		Protein, Gm per 100 Cc				Red Blood Cells, Millions per Cu Mm			Albumin in Urine	Dye Test	Size of Spleen					
		Total	Albumin	Globulin	Albumin Globulin Ratio	Non protein Nitrogen, Mgr per 100 Cc	Hemo globin, Gm per 100 Cc	Interle Index								
No	Name	1	E S	7.27	2.94	4.33	0.68	24.0	13.0	180	44 to 115	+	30	0	Stone in common duct, operation	Not obtained
2	J D	5.63	2.78	2.85	0.90	24.1	13.0	380	165	0	100	0	100	0	Stone in common duct	Biliary cirrhosis
3	G S	5.88	1.47	4.43	0.30	49.5	10.0	310	74	0	—	0	—	0	Stone in common duct, suppurative cholecystitis	Death
4	W P	6.65	3.46	3.19	1.08	30.0	12.0	420	37	0	—	0	—	0	Calculus cholecytitis, stone in cystic duct, operation	Recovery
5	B H	8.28	5.16	3.12	1.60	30.0	12.4	315	16	0	0	0	0	0	Calculus cholecytitis	Recovery
6	S C	7.63	4.52	3.01	1.15	30.0	9.9	490	160	0	90	0	90	0	Carcinoma of extra hepatic bile passages	Carcinoma of common bile duct
7	E S	6.96	3.50	3.46	1.00	30.0	9.5	240	107	0	80	0	80	0		Carcinoma of hepatic duct
8	S L	6.43	3.17	3.26	0.90	28.8	16.0	530	134	0	60	0	60	0		Carcinoma of common bile duct
9	G R	6.92	3.91	3.01	1.30	53.0	14.0	480	34	0	—	0	—	0	Carcinoma of extra hepatic ducts, operation	Carcinoma of head of pancreas
10	J F	6.48	3.57	2.91	1.20	18.0	10.0	310	150	0	45	+	45	+		Lobar pneumonia, cirrhosis
11	J R	7.57	4.23	3.34	1.27	26.0	10.0	350	75	0	—	0	—	0		Lobar pneumonia, cirrhosis
12	G M	5.64	1.86	3.78	0.46	30.0	10.5	320	40	0	—	+	—	—		
13	S H	5.74	2.80	2.94	0.90	113.9	15.0	480	90	0	—	+	—	0		
14	A K	4.40	1.83	2.57	0.71	74.9	15.0	480	18	Trace	—	0	—	0	Pneumonia	
15	E W	6.15	3.74	2.41	1.10	21.9	11.0	440	12	+	35	+	35	0	Catarrhal jaundice	
16	J F	6.90	4.20	2.70	1.50	30.0	14.0	460	55	0	—	0	—	0	Catarrhal jaundice	
17	N C	5.50	3.56	1.94	1.80	21.4	13.5	420	120	0	—	+	—	+	Catarrhal jaundice	
18	S M	6.74	4.60	2.14	2.15	22.6	15.0	460	95	0	—	0	—	0	Catarrhal jaundice	
19	E N	7.37	4.65	2.72	1.70	25.0	15.5	520	95 1/2	0	50	+	50	+	Catarrhal jaundice	
20	J B	6.54	3.71	2.05	1.30	61.0	15.0	510	125	0	80	+	80	+	Chronic hepatitis	
21	F W	5.83	3.13	2.73	1.10	20.5	12.5	430	29	0	60	0	60	0	Delirium tremens, alcoholic hepatitis	
22	J B	5.48	3.19	2.29	1.30	22.9	13.0	480	32	+	30	+	30	0		

was made. While two other patients presented the clinical history of alcoholic cirrhosis, studies of the blood protein showed a normal value for albumin, with a slight increase in the globulin content. The diagnosis was the hypertrophic form of compensated cirrhosis of the liver with adequate hepatic function.

SUMMARY AND CONCLUSIONS

In the literature there is abundant evidence that the liver plays an important rôle in the synthesis of serum albumin.

In decompensated portal cirrhosis there is a low value for serum albumin, with elevation of the globulin content and a reversal of the albumin-globulin ratio.

Evidence is offered that this alteration in the protein is not due to mechanical loss in ascitic fluid or restriction of the intake of protein and that it is not abolished by an increased protein content.

The alterations in the protein are attributed to hepatic damage and to the loss of the liver's ability to synthesize serum albumin.

In some cases the damage becomes so severe that an adequate intake of protein may lead to a more rapid progress of the disease. In such cases the liver has apparently lost its ability to detoxify protein metabolites.

In other forms of hepatic disease there is parallelism between the extent of hepatic damage and the alterations of the serum protein.

The determination of serum protein is often a helpful procedure in the diagnosis of obscure conditions in which there is hepatosplenomegaly.

ACUTE URANIUM NEPHROSIS

THE MECHANISM OF THE GLYCOSURIA

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AND

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Although the experimental nephrosis induced by uranium nitrate has been studied extensively, many of the factors influencing the excretion of urinary substances in this condition are still imperfectly understood

The present investigation was undertaken originally to demonstrate more clearly the mechanism of the glycosuria which occurs during the early stages of the nephrosis induced by uranium. Later the studies were extended to urinary substances other than sugar, and the output of nitrogen, chlorides and albumin was determined throughout the course of the nephrosis. The alterations in the excretion of the urinary substances were correlated with the changes in the concentration of some of these substances in the blood and with the anatomic alterations in the kidneys.

REVIEW OF THE LITERATURE

Most of the previous work on experimental uranium nephrosis has been reviewed in the excellent monograph of MacNider,¹ therefore, only the literature directly pertinent to the present report will be discussed. The occurrence of glycosuria and polyuria in the acute nephrosis following the administration of uranium nitrate was first observed by Chittenden, Hutchinson and Lambert.² Some workers (Meyner³ and Fleckseder⁴) said they considered the glycosuria to be secondary to an accompanying hyperglycemia, but it was shown by others (Lépine and

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1 MacNider, W de B. *Physiol Rev* **4** 595, 1924

2 Chittenden, R H, and Hutchinson, M T. *Tr Connecticut Acad Arts & Sc* **7** 261, 1887. Chittenden, R H, and Lambert, A. *Ztschr f Biol* **25** 513, 1889

3 Meyner, H. *Der Kohlehydratverbrauch bei Uranvergiftungen*, Inaug Dissert, Wurzburg, P Scheiner, 1898

4 Fleckseder, R. *Arch f exper Path u Pharmacol* **6** 54, 1907

Boulud,⁵ Blanck,⁶ Frank,⁷ Pollak⁸ and Wallace and Myers⁹) that the kidney in uranium poisoning could excrete sugar when the level of sugar in the blood was normal or even subnormal Pohl¹⁰ observed in his animals that, in addition to the glycosuria and polyuria reported by Chittenden, there was an increased excretion of chlorides Wallace and Myers, on the other hand, could find no relationship between the excretion of sugar and that of chlorides The kidneys of Pohl's animals showed severe tubular destruction, but the glomeruli were intact Austin and Eisenbrey¹¹ observed diuresis associated with an increased elimination of chlorides when small doses of uranium nitrate were given Later in the course of the poisoning the excretion of chlorides was reduced Weber¹² noted an increase in the volume of urine and a response to diuretics that were greater than in his normal controls From the work of Christian, Smith and Walker,¹³ Christian and O'Hare,¹⁴ Pearce,¹⁵ MacNider¹⁶ and Aschoff and Suzuki¹⁷ it is known that the injury induced by uranium is largely tubular and that the principal site of damage is the epithelium of the third and distal portion of the tubule The glomeruli are much less susceptible to injury, and it is only after several days of uranium poisoning that glomerular changes can be demonstrated histologically

METHODS AND MATERIAL

Twelve female dogs weighing from 6.25 to 17.75 Kg were used The animals fasted for a preliminary period of at least one day and for the entire course of the experiment but were allowed drinking water as desired

After a control period of from four hours to three days, each animal was given a single subcutaneous injection of uranium nitrate (15 mg per kilogram of body weight, except in one instance in which 10 mg per kilogram of body weight was given) Throughout the experimental and control periods frequent

5 Lepine, R, and Boulud *Rev de med*, Paris **24** 1, 1904

6 Blanck, S *Med Klin* **1** 1144, 1905

7 Frank, E *Arch f exper Path u Pharmakol* **72** 387, 1913

8 Pollak, L *Arch f exper Path u Pharmakol* **64** 415, 1911

9 Wallace, G B, and Myers, H B *J Pharmacol & Exper Therap* **5** 511, 1914

10 Pohl, J *Arch f exper Path u Pharmakol* **67** 233, 1912

11 Austin J, and Eisenbrey, A B *J Exper Med* **14** 366, 1911

12 Weber, S *Arch f exper Path u Pharmakol* **54** 1, 1906

13 Christian, H A, Smith, R M, and Walker I C *Experimental Cardio-renal Disease, Arch Int Med* **8** 468 (Oct) 1911

14 Christian, H A, and O'Hare, J P *J M Research* **28** 227, 1913

15 Pearce, R M *The Problems of Experimental Nephritis, Arch Int Med* **5** 133 (Feb) 1910

16 MacNider, W de B *Am J M Sc* **178** 449, 1929

17 Aschoff, L, and Suzuki *Verhandl d deutsch path Gesellsch* **15** 199, 1912

determinations were made of the sugar, urea or nonprotein nitrogen content of the blood and the sugar and total nitrogen contents of the urine. Likewise, in two experiments the urinary output of albumin and chlorides was quantitatively determined.

The animals were kept in metabolism cages which permitted accurate collections of all urinary specimens. At the end of each experimental period the animals were catheterized. The bladder was rinsed thoroughly with a measured amount of sterile water, and the volume of urine was estimated. The amount of drinking water ingested during each period was determined.

Seven of the animals were permitted to live until anuria developed and death occurred, four animals were killed with rapid chloroform anesthesia when the glycosuria was estimated to be at its greatest height and one dog was killed at the onset of the anuric stage. Immediately after the death of the animals the kidneys were removed and placed in a dilute solution of formaldehyde U S P (1:10).

The total nitrogen content of the urine was determined by the usual macro-method of Kjeldahl, the nonprotein nitrogen content of the blood by the micro-method of Kjeldahl, the urea content of the blood by the method of Folin and Denis, the sugar content of the urine by the procedures of Benedict and of Shaffer and Hartmann and the sugar content of the blood by the method of Shaffer and Hartmann. The Volhard-Arnold method was used for the determination of the urinary chlorides. The quantitative estimation of the urinary albumin was accomplished by determining the reduction in the amount of total nitrogen in the urine when the albumin was removed. The albumin was removed by boiling the urine after acidification with acetic acid. The filtrates of all specimens of urine treated in this manner showed no albumin.

The renal tissue was fixed in solution of formaldehyde, sectioned by the paraffin technic and stained with hematoxylin and eosin.

For the sake of economy of space, detailed protocols are not presented. Instead, charts showing data observed in typical experiments are given. These data are representative of all the observations, as the findings in the comparable experiments were essentially the same.

OBSERVATIONS

Stage of Glycosuria—In all experiments sugar first appeared in the urine at about the sixth hour after the administration of the uranium nitrate. By the tenth hour the glycosuria had become well established, and at about the twenty-fourth hour the excretion had reached its maximum of from 0.128 to 0.314 Gm of sugar per hour. Thereafter, it decreased steadily, and at about the thirty-sixth to the seventy-second hour the glycosuria disappeared. Accompanying the glycosuria was an increase in the volume of urine. As the glycosuria decreased the volume of urine became smaller, and in most instances anuria developed rapidly. However, in one experiment moderate amounts of urine continued to be excreted for twenty-seven hours after the glycosuria had disappeared.

In no experiment did the concentration of blood sugar during the period of glycosuria rise above the normal control values. On the other hand, there was a slight decrease in the level of the blood sugar

in most instances while sugar was being excreted by the kidneys. Figure 1 shows this relationship and is representative of the findings in all the experiments. In the two animals for which the excretion of chlorides was determined, the urinary chloride content was observed to increase at about the same time that glycosuria was established. Thus for dog

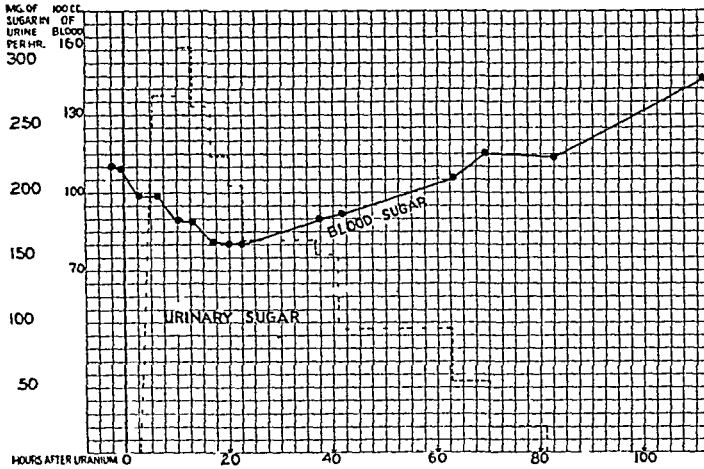


Fig 1 (dog 189) —The effect of uranium nitrate on the level of the blood sugar and on the urinary excretion of sugar

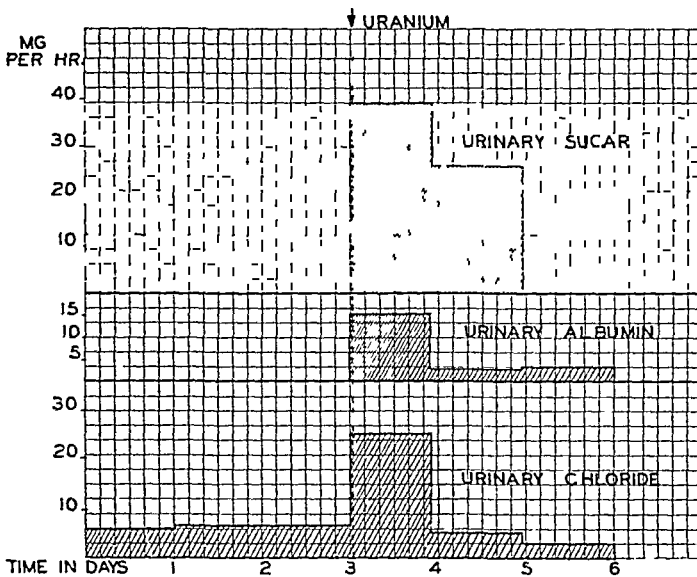


Fig 2 (dog 225) —The excretion of urinary chlorides, sugar and albumin after the administration of uranium nitrate

224 the urinary chloride content increased from 0.006 Gm per hour (calculated as sodium chloride) to 0.019 Gm per hour during the period of twenty-three hours in which from 0.06 to 0.043 Gm of sugar was being eliminated hourly by the kidneys. However, the glycosuria of both dogs persisted for about twenty-four hours after the excretion

of chloride had returned to its former level or had decreased to a level lower than that of the control period. Figure 2 illustrates the data for dog 225, which are essentially similar to those observed for dog 224.

The urine contained albumin as early as the third hour following the administration of uranium nitrate. The albuminuria preceded the establishment of the glycosuria and persisted until the animals became anuric. The excretion of albumin appeared to bear no relation to the glycosuria. Thus, in the experiment on dog 225, 0.015 Gm of albumin nitrogen was excreted per hour, while 0.039 Gm of sugar was being eliminated per hour by the kidneys. However, in the following period, when 0.026 Gm of sugar was still being excreted each hour, the output of albumin nitrogen had fallen to 0.002 Gm per hour (fig. 2).

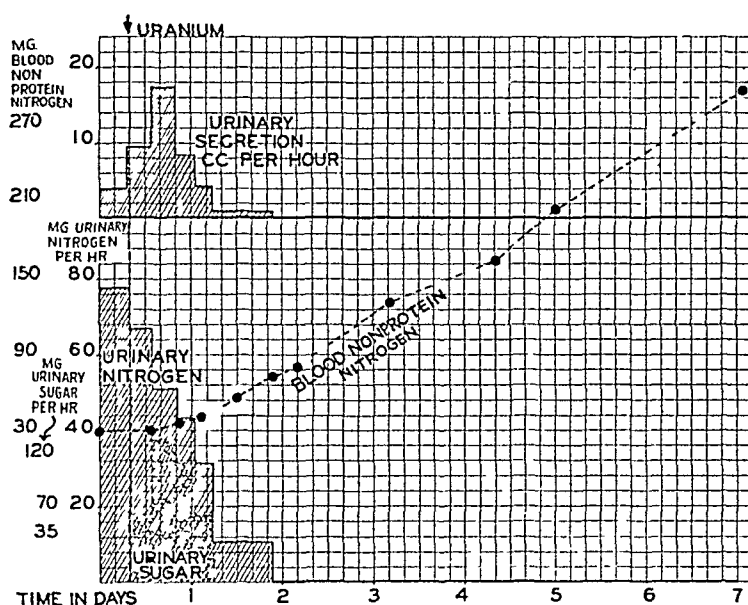


Fig. 3 (dog 197).—The effect of uranium nitrate on the volume of urine, on the excretion of total urinary nitrogen and sugar and on the level of nonprotein nitrogen in the blood. The relationships between the changes in the volume of urine and those in the content of urinary sugar and between the changes in the urinary nitrogen and those in the nonprotein nitrogen of the blood are shown.

The development of albuminuria preceded any increase in the concentration of urea or nonprotein nitrogen in the blood. For example, in dog 197 the blood urea was of normal value twenty-four hours after the injection of uranium nitrate, although both albuminuria and glycosuria had been well established for over six hours. After this period the concentration of nonprotein nitrogen in the blood increased gradually until glycosuria had disappeared and anuria had developed. After the establishment of anuria the rise in the nonprotein nitrogen level of the blood was rapid (fig. 3).

The kidneys of all four dogs killed when the glycosuria was estimated to be at its height showed similar histologic changes. The main site of

damage was the convoluted tubules. There was beginning degeneration, with cloudy swelling of the epithelium of the convoluted tubules, but no actual necrosis. There was moderate congestion throughout the

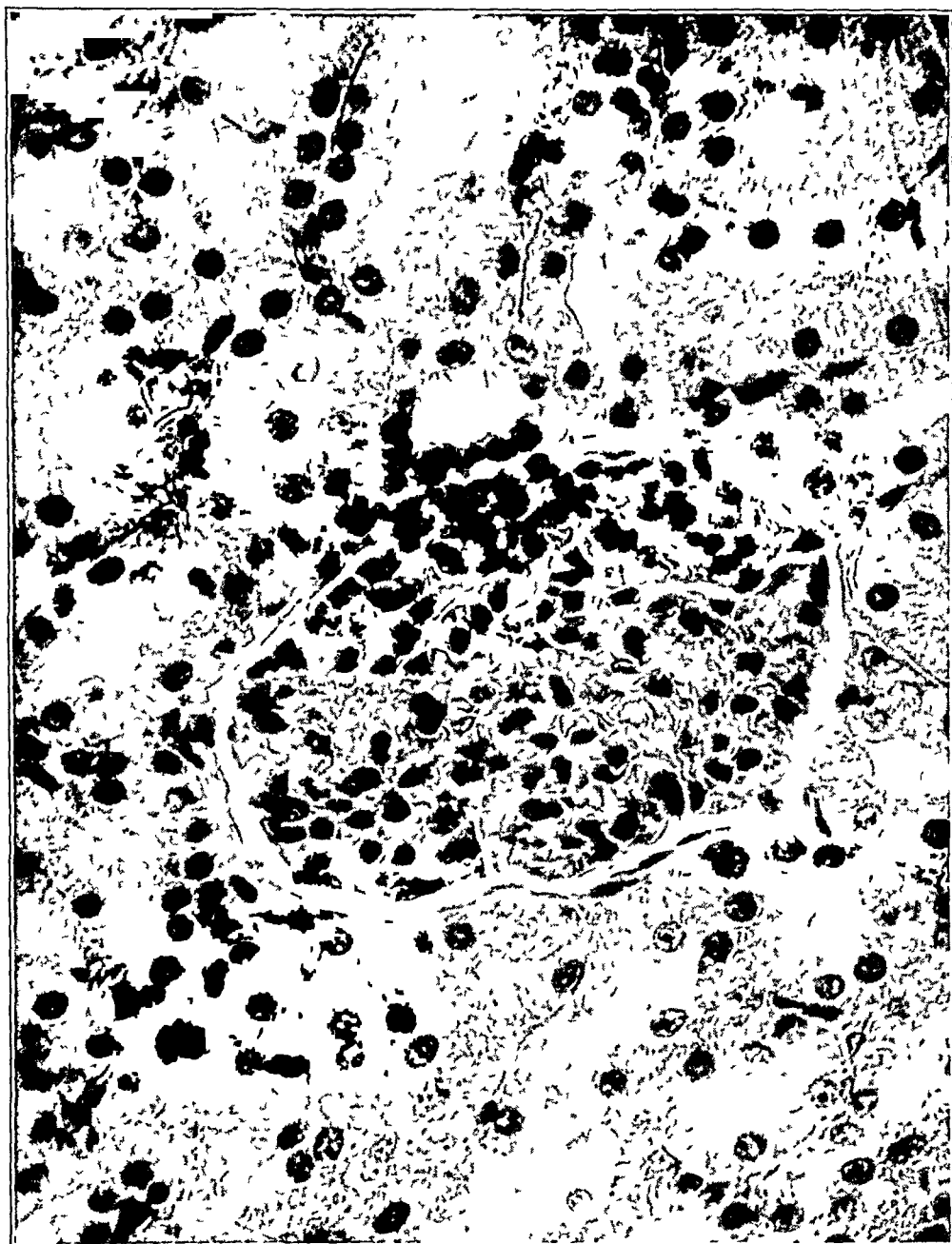


Fig 4 (dog 194) —Stage of glycosuria. Section of the kidney twenty-four hours after the administration of uranium nitrate. The urinary excretion of sugar was 0.272 Gm per hour, and the sugar content of the blood was 98 mg per hundred cubic centimeters.

kidney, including the glomeruli, but the glomeruli otherwise appeared to be normal (fig 4).

State of Anuria—In all eight animals which were permitted to live after the glycosuria had disappeared anuria developed in the course of a few days. Although the urinary output diminished as the glycosuria

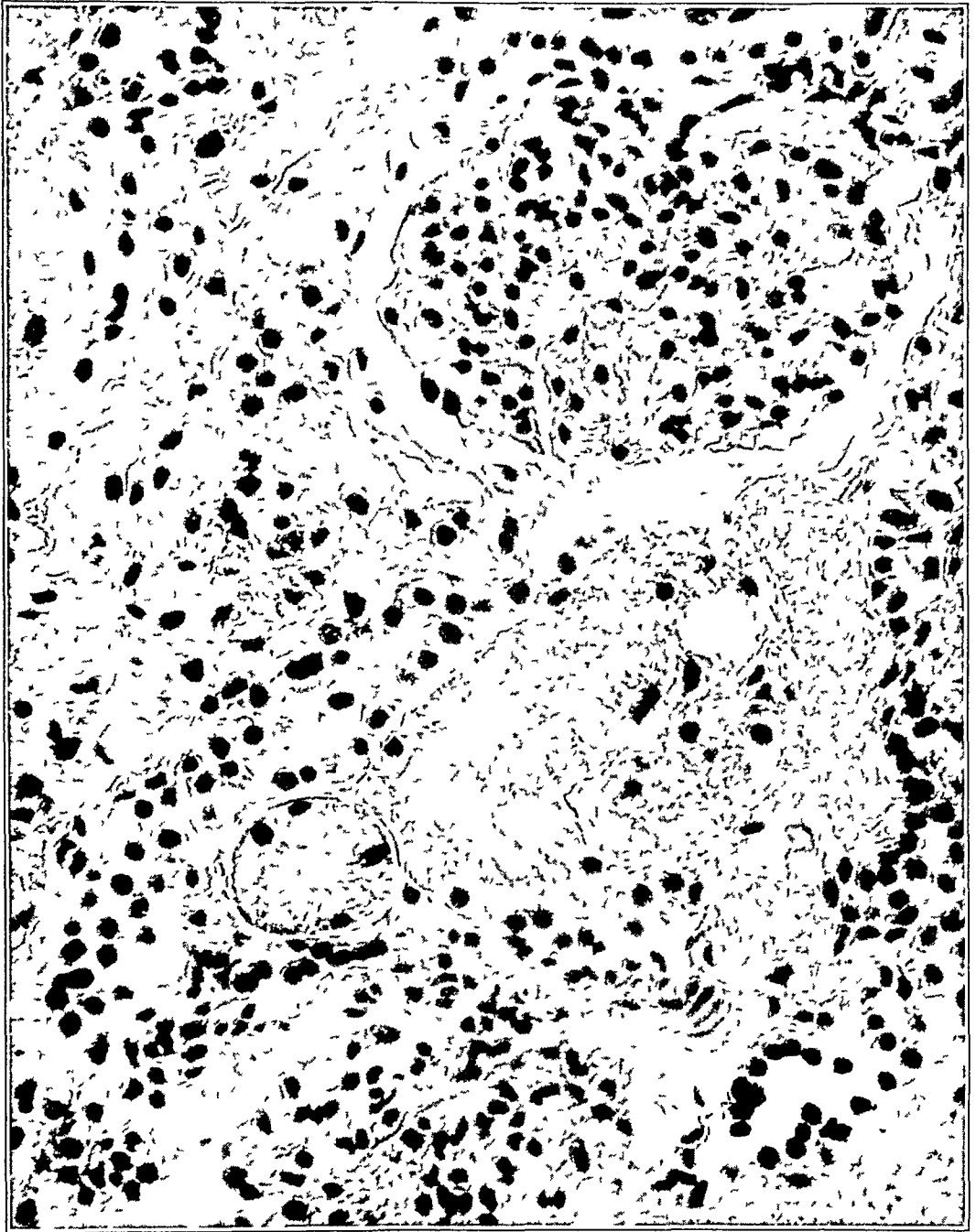


Fig 5 (dog 191)—Stage of anuria. Section of the kidney nine days after the administration of uranium nitrate.

decreased, the volume of urine did not fall below the level of the control period until the glycosuria had disappeared. Thereafter, the development of anuria proceeded rapidly.

After the establishment of anuria the concentration of nonprotein nitrogen in the blood increased rapidly until shortly before the death of the animal, when there was as much as 299 mg of nonprotein nitrogen in each hundred cubic centimeters of blood. The concentration of

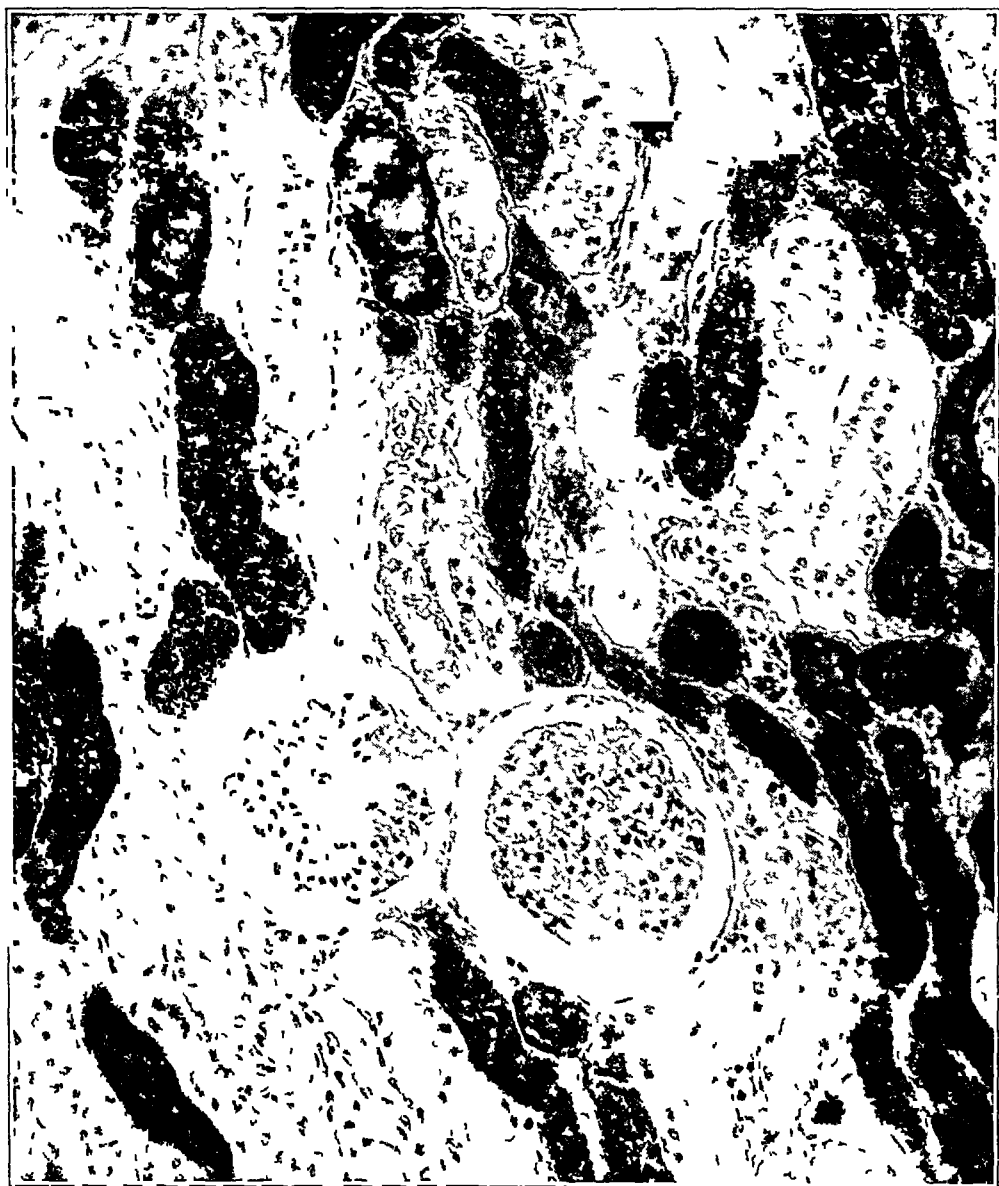


Fig 6 (dog 192) —Stage of anuria. Section of the kidney eight days after the administration of uranium nitrate, showing calcium deposition (black). The dog was anuric for six days. There was 150 mg of sugar per hundred cubic centimeters of blood.

sugar in the blood likewise rose, although the increase was much less rapid. It increased steadily and reached an average value of 128 mg per hundred cubic centimeters. The kidneys of all the animals dying

in the anuric stage showed essentially the same anatomic changes. In dog 192, which lived for six days after total anuria had been established, the pathologic alterations were more advanced than in the other seven animals in this group. The main site of injury was the convoluted tubule. Necrosis and desquamation of the epithelium were noted, with fusing of the cells and obliteration of their margins. Many of the cells were without nuclei. In some places granular debris filled the lumens of the tubules, and vacuoles of varying sizes were noticeable in the epithelial debris. In dog 192 there was considerable calcium formation in the convoluted tubules, the picture resembling that seen in mercury bichloride poisoning. In the other animals in this group early deposition of calcium was seen in the tubules. The straight tubules, on the whole, were uninvolved, except for occasional early fatty degeneration of the epithelium. The glomeruli in these animals were only moderately involved. There was moderate congestion with hemorrhages, and in some places the tufts were shrunken and had pulled away from Bowman's capsule. Occasional hyaline droplets were seen in the lumen of the capsule. On the whole, the glomeruli were well preserved.

COMMENT

The experiments indicate that the glycosuria occurring early in the course of acute nephrosis induced by uranium is of renal origin and is related to early injury to the tubular epithelium. Moreover, the increase in the excretion of water and chlorides could be ascribed to the same changes. Wearn and Richards¹⁸ have shown that in the frog water, sugar and chlorides are reabsorbed from the glomerular filtrate by the tubules. An impaired ability of the tubular epithelium to reabsorb these constituents in uranium poisoning would explain the results observed in these experiments. Such an explanation would be compatible with the changes demonstrated by histologic examination. The functional alterations in this stage of the nephrosis appear to be similar to those observed in phlorhizin poisoning (Deuel, Wilson and Milhorat¹⁹ and Richards²⁰) and in nephrosis occurring in patients (Hawkins, MacKay and Van Slyke²¹). The latter investigators found the kidneys to be abnormally permeable to dextrose in the "tubular" type of nephritis (nephrosis with considerable albuminuria), whereas in the glomerulo-

18 Wearn, J. T., and Richards, A. N. *Am J Physiol* **71** 209, 1924

19 Deuel, H. J., Wilson, H. E. C., and Milhorat, A. T. *J Biol Chem* **74** 265, 1927

20 Richards, A. N., in *Harvey Lectures, 1934-1935*, Baltimore, Williams & Wilkins Company, 1936, p. 93

21 Hawkins, J. A., MacKay, E. M., and Van Slyke, D. D. *J Biol Chem* **78** xxiii, 1928

nephritic type no glycosuria developed after the administration of dextrose unless there was a considerable increase in the sugar content of the blood

The urinary changes occurring late in the course of the poisoning (the retention of the various urinary substances and finally the complete anuria) can find a partial explanation in the idea advanced by MacNider,²² who stated that he thought the anuria was the result of occlusion of the lumen of the tubules by debris. On the other hand, the mechanism in uranium poisoning is probably similar to that observed by Richards²³ following the administration of mercury bichloride in frogs. In frogs poisoned with mercury, Richards demonstrated a normal glomerular function, but the resorption of the glomerular filtrate proceeded at such a rapid rate that anuria resulted. However, the early retention of nitrogen might conceivably be due to the glomerular changes, as was suggested by Milhorat and Deuel²⁴

SUMMARY

The urinary changes and the anatomic alterations in the kidneys were studied during the various stages of the acute nephrosis induced by uranium nitrate. Dogs given large doses of uranium showed evidence of extensive renal involvement within a few hours after injection of the salt.

Glycosuria appeared early and was accompanied with an increase in the urinary elimination of water and chlorides. In the main, these changes occurred concomitantly. During the periods when the glycosuria was at its height, larger amounts of water and chlorides were eliminated, whereas the urine contained smaller amounts of water and chloride during the period in which the glycosuria decreased and finally disappeared. The level of the blood sugar during this stage remained normal or fell to slightly subnormal values. The histologic alterations in the kidneys were confined to early degenerative changes in the tubular epithelium and suggest that the changes in the urinary elimination of sugar, water and chlorides are due to an impaired ability of the tubules to resorb these substances from the glomerular filtrate.

Albuminuria occurred early, but unlike the glycosuria, which disappeared after a few days, it persisted as long as urine was being excreted. The output of nitrogen was progressively decreased. This impairment was followed by an increase in the concentration of nonprotein nitrogen in the blood.

22 MacNider, W. de B. *J. Pharmacol. & Exper. Therap.* **3**: 423, 1912.

23 Richards, A. N. *Methods and Results of Direct Investigations of the Function of the Kidney*, Baltimore, Williams & Wilkins Company, 1929.

24 Milhorat, A. T., and Deuel, H. J., Jr. *Proc. Soc. Exper. Biol. & Med.* **25**: 294, 1928.

Anuria developed soon after the glycosuria had disappeared. Shortly after the establishment of anuria the amount of nonprotein nitrogen in the blood increased rapidly, and the sugar content of the blood rose to above its previous level. The kidneys at this stage showed advanced degeneration of the tubular epithelium and only moderate changes in the glomeruli. It is suggested that the anuria might be due to the complete resorption of the glomerular filtrate by the damaged tubules.

Dr. Elise L'Esperance, of the Department of Pathology, assisted in preparing and interpreting the microscopic slides.

CARCINOMA OF THE ISLANDS OF LANGERHANS WITH HYPOGLYCEMIA AND HYPER- INSULINISM

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The syndrome commonly known as spontaneous hypoglycemia was recognized by Seale Harris¹ in 1924 and was attributed by him to "hyperinsulinism," in contrast to the supposed "hypo-insulinism" of diabetes. The possibility of true hyperinsulinism was first demonstrated in 1927 by Wilder, Allan, Power and Robertson² in a report of a case of severe hypoglycemia in which carcinoma of the islands of Langerhans with extensive metastasis to the liver and lymph nodes was noted at necropsy. The cells of the metastatic nodules in the liver bore a striking resemblance to the cells of the islands of Langerhans, and an extract of the hepatic nodules was found to possess the property of markedly lowering the concentration of sugar in the blood when injected into rabbits.

Since that report there have appeared in the literature (recently reviewed by Whipple and Frantz³ and by Wilder⁴) numerous descriptions of cases of spontaneous hypoglycemia. In several instances the condition has been attributed to hyperfunctioning adenomas of the islands of Langerhans, since surgical removal of one or more tumors from the pancreas resulted in complete recovery and cessation of symptoms. The first case of this kind was that of Howland, Campbell,

* From the Division of Biochemistry, the Mayo Foundation

1 Harris, Seale. Hyperinsulinism and Dysinsulinism, J A M A **83** 729-733 (Sept 6) 1924

2 Wilder, R M, Allan, F N, Power, M H, and Robertson, H E. Carcinoma of the Islands of the Pancreas. Hyperinsulinism and Hypoglycemia, J A M A **89** 348-355 (July 30) 1927

3 Whipple, A O, and Frantz, Virginia K. Adenoma of Islet Cells with Hyperinsulinism. A Review, Ann Surg **101** 1299-1335 (June) 1935

4 Wilder, R M. Spontaneous Hypoglycemia, Internat Clin **3** 143-163 (Sept) 1936

Maltby and Robinson⁵ (1929) The tumor was extracted for insulin, and the extract was tested on mice by Professor C H Best Of eight mice which were given injections, five had insulin convulsions, and two of the animals died The extract thus undoubtedly contained insulin, but accurate assay was not attempted, because of lack of material as well as lack of any accurate knowledge of the amount of insulin extractable from the normal pancreas of man In the other cases in which removal of an island cell tumor from the pancreas has resulted in cure of the hypoglycemic condition, the tissue removed has been extracted in three instances (Graham and Womack,⁶ 1933, Derick, Newton, Schulz, Bowie and Pokorny,⁷ 1933, and Liu, Loucks, Chou and Chen,⁸ 1936), and more or less conclusive evidence has been obtained of the presence of insulin activity in the extracts

Tumors removed at operation in some of these cases were considered to be carcinomas with a low grade of malignancy (Howland and others⁵ and Graham and Womack⁶), but only four cases of carcinoma of the islands of Langerhans with metastasis to the liver have been described The first of these, subsequent to the case of Wilder, Allan, Power and Robertson,² was reported by Hamdi,⁹ who discovered the carcinoma at necropsy The metastatic nodules in the liver resembled morphologically the islands of Langerhans in the pancreas However, there was no clinical history of the syndrome of hypoglycemia, and the metastatic growths were not examined for insulin In the second case, that of Judd, Faust and Dixon,¹⁰ there was a definite history of the hypoglycemic syndrome, and a specimen taken for biopsy from a carcinomatous nodule in the liver was histologically characteristic of an island cell tumor Examination of the tissue for insulin was not attempted The third case, reported

5 Howland, Goldwin Campbell, W R , Maltby, E J , and Robinson, W L Dysinsulinism Convulsions and Coma Due to Islet Cell Tumor of the Pancreas, with Operation and Cure, *J A M A* **93** 674-679 (Aug 31) 1929

6 Graham, E A , and Womack, N A The Application of Surgery to the Hypoglycemic State Due to Islet Tumors of the Pancreas and to Other Conditions, *Surg, Gynec & Obst* **56** 728-742 (April) 1933

7 Derick, C L , Newton, F C , Schulz, R Z , Bowie, M A , and Pokorny, N A Spontaneous Hyperinsulinism Report of a Case of Hyperinsulinism Cured by Surgical Intervention, *New England J Med* **208** 293-298 (Feb 9) 1933

8 Liu, S H , Loucks, H H , Chou, S K , and Chen, K C Adenoma of Pancreatic Islet Cells with Hypoglycemia and Hyperinsulinism Report of a Case with Studies on Blood Sugar and Metabolism Before and After Operative Removal of Tumor, *J Clin Investigation* **15** 249-260 (May) 1936

9 Hamdi, H Ein insulargenetisches Pankreascarcinom (Insulom), *Ztschr f Krebsforsch* **37** 411-413, 1932

10 Judd, E S , Faust, L S , and Dixon, R K Carcinoma of the Islands of Langerhans with Metastasis to the Liver Producing Hyperinsulinism Report of Case, *West J Surg* **42** 555-557 (Oct) 1934

by Bickel, Mozer and Junet,¹¹ was an interesting one, that of a man who had had severe diabetes for more than a year and who suddenly showed a tendency toward persistent and marked hypoglycemia associated with attacks of unconsciousness. At necropsy a carcinoma of the pancreas was present, with multiple metastatic growths in the liver. The cellular structure of the growths was similar to that of the islands of Langerhans. An extract of the tumor of the pancreas when tested on dogs was found to contain "insuline en quantite notable," but concerning extracts of the metastatic growths in the liver the report was "absence d'insuline." No details concerning the procedure for extraction and testing were given.

To these cases we are now able to add a fifth one, of carcinoma of the islands of the pancreas with metastasis to the liver. This case is one of spontaneous hypoglycemia, attributable probably to true hyperinsulinism, since tests of extracts of the metastatic nodules in the liver gave unequivocal evidence of insulin-like activity. The studies we have made confirm the observations reported in the case of Wilder and his associates and constitute, we believe, the second demonstration of the presence of insulin in malignant tissue originating from the islands of Langerhans but not situated directly in the pancreas itself.

REPORT OF A CASE

A married woman, 41 years of age, came to the Mayo Clinic on Jan 30, 1935, having been referred by Dr L E Cooley, of Dubuque, Iowa, who had made the diagnosis. She had been in excellent health until three months previously, at which time she had noticed that on arising in the morning she felt light headed, dizzy and slightly confused mentally. Often there was associated profuse perspiration, and the entire syndrome lasted from two to three hours, after which it gradually disappeared. Soon after the onset of this condition, the patient discovered that a glass of milk taken in the course of the attack would give partial relief. However, at that time she did not realize that her habit of not eating breakfast was associated with these attacks.

On December 1, a month after the onset of her symptoms, she was busy preparing for a large dinner party and did not take time to eat in the course of the day. A few minutes after she took her seat at the table that evening she was overcome by a feeling of extreme weakness. This sensation was almost immediately accompanied with marked mental confusion and by profuse perspiration. Fifteen minutes later she became completely unconscious, with associated generalized muscular rigidity, which was more marked in the right arm and leg. She remained in this state for four hours and then without treatment gradually recovered. The only residual manifestation was moderate weakness of the right arm and leg. The

11 Bickel, Georges, Mozer, J J, and Junet, R. Diabete avec denutrition grave. Disparition de la glycosurie et attenuation progressive de l'hyperglycemie a la suite du developpement d'un carcinoma insulaire du pancreas avec metastases hepatiques massives, Bull et mem Soc med d hôp de Paris 51 12-21 (Jan 11) 1935

following day she did not feel well and therefore remained in bed and ate nothing. That evening she again lost consciousness in a manner similar to that of the previous night, and she remained in a comatose state for thirty hours. At the end of this period her condition became alarming, and as supportive treatment she was given solution of dextrose intravenously. The injection restored her to full consciousness almost immediately. However, weakness of the right side remained, as did slight thickness of speech, several hours longer. Her illness was then recognized as a state of spontaneous hypoglycemia, and she was consequently given frequent feedings of a diet high in carbohydrate. On this regimen she experienced no more attacks, except for a mild attack one morning, which was attributable to delay in eating breakfast. The level of blood sugar at that time was found to be 30 mg per hundred cubic centimeters. The patient said that by trial and error she had determined that the maximal time over which she could remain free from symptoms between feedings was from ten to twelve hours.

The past history was not remarkable except for hysterectomy and oophorectomy on the left side performed in 1933 for leiomyomas of the uterus. Physical examination disclosed nothing abnormal except increased deep reflexes. The edge of the liver was not palpable, and no abdominal masses were felt. The blood pressure

TABLE 1—*Data Showing the Effect of Dextrose*

Time	Blood Sugar, Mg per 100 Cc
8 00 a m	40
57 Gm of dextrose (orally)	
8 30 a m	132
9 00 a m	112
10 00 a m	146
11 00 a m	59

was 142 mm of mercury systolic and 94 diastolic. The urine was analyzed many times and was found to contain albumin varying between grade 1 and grade 2, with an occasional pus cell. The erythrocyte count was 4,380,000 and the leukocyte count 7,500 cells per cubic millimeter of blood. The differential count was 75 per cent neutrophils, 19.5 per cent lymphocytes, 5 per cent monocytes and 0.5 per cent eosinophils. A Wassermann test of the blood gave a negative reaction. The blood showed 14 mg of urea and 2.43 mg of uric acid per hundred cubic centimeters. A roentgenogram of the skull appeared normal. The results of a dextrose tolerance test were definitely significant. The level of blood sugar during fasting was 40 mg per hundred cubic centimeters. Two hours after the oral administration of 57 Gm of dextrose it rose to 146 mg, but one hour later it had again receded to 59 mg per hundred cubic centimeters (table 1). If food was withheld for longer than ten hours, symptoms of hypoglycemic shock developed. At the end of that interval the patient would become nervous and confused, and if carbohydrate were not administered immediately she would quickly pass into a semicomatose state. This observation verified the patient's own statement.

3 In order to determine the presence and availability of the store of glycogen in the liver, epinephrine and solution of posterior pituitary (double U S P strength) were injected subcutaneously in two different studies (tables 2 and 3). The definite rise in the level of blood sugar after the injection of epinephrine was felt to be evidence that glycogen was being discharged into the blood stream from the liver. However, the solution of pituitary had no effect, and the blood sugar level

continued to fall, so that at the end of two hours it became necessary to administer orange juice and milk in order to avoid a hypoglycemic reaction. The function of the liver was found to be unimpaired, as disclosed by the bromsulphalein tolerance, the galactose tolerance and the hippuric acid test. The van den Bergh reaction was direct, and the value for serum bilirubin was 1 mg per hundred cubic centimeters.

Because the patient was suffering definite attacks of spontaneous hypoglycemia and because there was no evidence of impairment in the ability of the liver to store and discharge glycogen it was felt that a state of hyperinsulinism existed, due probably to excess secretion caused by a neoplasm of the islands of Langerhans. Therefore, on February 6, after intravenous administration of 100 Gm of dextrose, Dr Judd performed an abdominal exploratory operation. The liver was found to contain numerous carcinomatous metastatic growths. The pancreas was so sur-

TABLE 2—*Data Showing the Effect of Epinephrine*

Time	Blood Sugar, Mg per 100 Cc
3 00 p m	85
1 cc of solution of epinephrine hydrochloride (1 1,000), subcutaneously	
4 00 p m	117
5 00 p m	89

TABLE 3—*Data Showing the Effect of Solution of Pituitary*

Time	Blood Sugar, Mg per 100 Cc
3 00 p m	73
1 cc of solution of pituitary (intramuscularly)	
3 30 p m	58
4 00 p m	50
5 00 p m	100*

* Orange juice and milk given ten minutes before specimen of blood was taken

rounded by dense masses of enlarged lymph nodes that it was impossible to determine definitely whether or not that organ was the site of the primary carcinoma. Microscopic examination of a specimen removed from the liver verified the diagnosis of carcinoma, probably primary in the islands of Langerhans. The operation was performed with the patient under spinal anesthesia, the entire procedure lasted twenty-five minutes and was completed at 10 15 a m. At 10 50 a m the concentration of blood sugar was 133 mg per hundred cubic centimeters, and at 1 p m 102 mg, and by 3 p m it had fallen to 92 mg. Dextrose solution was then administered intravenously every ten hours, and after forty-eight hours the patient was again given the preoperative diet. An uneventful recovery ensued, and she was dismissed from the clinic on February 25. She died in Salt Lake City on July 10.

Gross Postmortem Observations—Necropsy was performed by one of us (M C L) at Salt Lake City approximately one hour after death had occurred. The heart was normal. The lungs revealed a slight amount of passive congestion. The liver contained innumerable firm, reddish gray nodules varying from 0.5 to 4 cm in diameter, so that the entire organ was enlarged to approximately one and

a half times its normal size. The pancreas was surrounded by a mass of enlarged lymph nodes which were of firm consistency and reddish on the cut surface. The pancreas itself contained no nodules but was unusually firm. Both the pancreatic and the common bile duct were patent. The lymph nodes in the region of the mesentery and along the course of the abdominal aorta also were enlarged and of the same texture and color as those surrounding the pancreas. The gastric mucosa contained multiple large ecchymotic areas in its mucosal surface. The uterus, both fallopian tubes and the left ovary were absent. The right ovary contained a hemorrhagic cyst, approximately 3 cm in diameter. The other abdominal viscera were not remarkable. Immediately after completion of the examination, the entire right lobe of the liver, half the pancreas and a mass of the enlarged lymph nodes were packed in solid carbon dioxide and shipped to Rochester, Minn., by airplane. On arrival they were solidly frozen and in a state of perfect preservation. The liver was immediately sectioned, and portions to be extracted were excised. Sections for microscopic study were taken from numerous areas in the tail of the pancreas, lymph nodes and liver and were fixed in Orth's solution. They were then blocked in paraffin and stained with hematoxylin and eosin. Portions of the liver were fixed in alcohol and stained for glycogen with Best's carmine dye.

Microscopic Postmortem Observations—The normal pancreatic tissue was extensively replaced by masses of tumor cells which were arranged almost entirely in islands and thin strands (fig 1A). The islands varied in size from that of a normal pancreatic island to that of an island at least twenty times larger. They were roughly circular in outline, and their cells were closely packed. In other areas fibrous connective tissue trabeculae separated the tumor cells into short thin strands. Nowhere was there any evidence of an attempt to form ducts or acini. Each group of tumor cells was surrounded by a clear space, lined with endothelial cells and frequently containing erythrocytes. However, there was no pronounced increase in the vascularization of the neoplastic tissue. The cellular characteristics were those of a moderately slow-growing carcinoma, with cells of uniform size and only a sparse scattering of large cells and mitotic figures. No multinucleated giant cells were seen, and the nuclei were not remarkably hyperchromatic. The absence of necrosis in the centers of the masses of tumor cells was evidence that cellular proliferation was not destroying the blood supply. Normal pancreatic acini were seen in only small areas and were surrounded by heavy masses of fibrous tissue, which appeared to be slowly choking them. In these areas there were also a few normal islands of Langerhans. One of the most striking features of the microscopic study was the difficulty experienced in differentiating the tumor islands from the normal islands.

All the lymph nodes which were sectioned were composed almost entirely of carcinoma, a few thin strands of lymphocytes around the periphery being the only certain means of identifying them. The distribution and cellular structure of the carcinoma in the nodes were practically identical with those of the growth in the pancreas.

The tumorous growths in the liver (fig 1B) revealed a most unusual histologic picture. In addition to the large, grossly visible metastatic growths there were innumerable cancerous nodules of microscopic size. They were circular to oval, with the cells packed in solid masses and with no tendency to form acini, thus giving the tumor nodules the appearance of large pancreatic islands. Each of the islands was sharply delineated by an encircling clear space, which could not be definitely identified as a blood vessel because of the absence of erythrocytes within its lumen. The larger island-like metastatic growths had undergone central

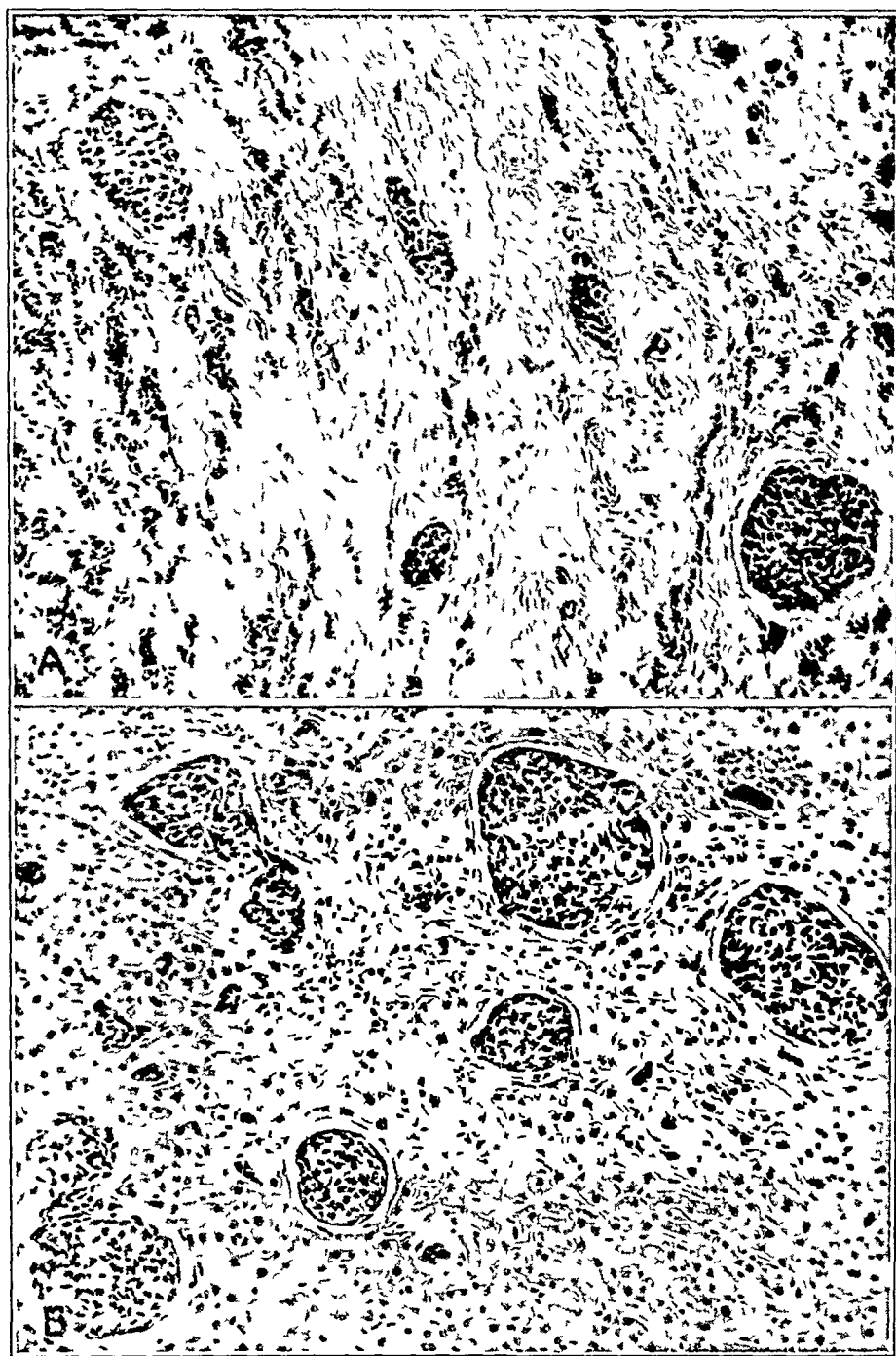


Fig 1—*A*, islet cell carcinoma in the pancreas *B*, metastasis in the liver from an islet cell carcinoma in the pancreas, $\times 125$

necrosis, and only a band of intact cells remained around the periphery. The cells in the more extensive areas of tumor had been compressed into elongated strands by heavy sheets of hyalinized fibrous tissue, and in these areas many capillaries were visible. The carcinoma in the liver appeared to be more malignant than in either the pancreas or the lymph nodes. The cells were more irregular in size and shape, and there were numerous giant cells, some of which were multinucleated. Mitotic figures were more plentiful, and all the nuclei were deeply basophilic.

From the morphologic standpoint it appeared that the tumor had originated as a slow-growing neoplasm in the pancreas, and later, as the speed of growth had increased, it had spread to the surrounding lymph nodes and finally to the liver, where it exhibited itself in the full bloom of a rapidly growing carcinoma. Robertson examined the microscopic sections and was of the opinion that this tumor had grown more slowly than the one which occurred in the case described in 1927² and that its morphologic appearance was even more characteristic of tumor of the islands of Langerhans than was that of the other tumor.

At the time the liver was originally sectioned four specimens had been taken from widely separated areas, these had been fixed in absolute alcohol and then stained with Best's carmine dye. They were bright pink, thus proving the presence of large deposits of glycogen. No quantitative analysis for glycogen was carried out.

Extraction of Metastatic Nodules of the Liver for Insulin—The method of extraction used was that of Best, Jephcott and Scott,¹² a procedure which they described as yielding the "maximal amounts of insulin from the pancreas." The cancerous tissue was carefully separated from the frozen liver, 127 Gm being finely ground and placed immediately in acid alcohol. At the same time 112 Gm of adjacent normal-appearing hepatic tissue was freed of cancer nodules as completely as possible and treated similarly. Each extract when completed was made up to a volume of 200 cc. For testing, four rabbits (1 to 4) weighing 2, 2.5, 2.6 and 2.3 Kg, respectively, were selected and made to fast for twenty-four hours. Rabbits 1 and 2 were given subcutaneous injections of 10 cc of the extract of the normal tissue of the liver (liver extract), and rabbits 3 and 4 were given 5 cc of the extract of cancerous tissue of the liver (tumor extract). The level of the blood sugar before and at intervals after injection was determined by the method of Folin and Malmros¹³ from 0.1 cc samples of blood drawn from the marginal vein of the ear. After six days the experiment was repeated, this time rabbits 1 and 2 being given 15 cc of the tumor extract and rabbits 3 and 4 15 cc of the liver extract.

The levels of blood sugar before and after injection in these two series of experiments are shown in figures 2 and 3. It is to be noted, first, that the values for blood sugar during fasting were all within normal limits, the highest being less than 130 mg per hundred cubic centimeters, and, second, that remarkably small changes in the concentration of blood sugar occurred after the injections of liver extract. This was to be expected, since it has been established by the work of

12 Best, C. H., Jephcott, C. M., and Scott, D. A. Insulin in Tissues Other Than the Pancreas, *Am. J. Physiol.* **100**: 285-294 (April) 1932.

13 Folin, Otto, and Malmros, H. An Improved Form of Folin's Micro Method for Blood Sugar Determinations, *J. Biol. Chem.* **83**: 115-120 (July) 1929.

Best, Jephcott and Scott that normal hepatic tissue, as well as animal and vegetable tissues in general, does not contain insulin that can be extracted by the methods now available. Consequently, the curves obtained after the injection of the inactive liver extracts serve as excellent controls and illustrate the small fluctuations in blood sugar level under the conditions of our experiments. In contrast to these control

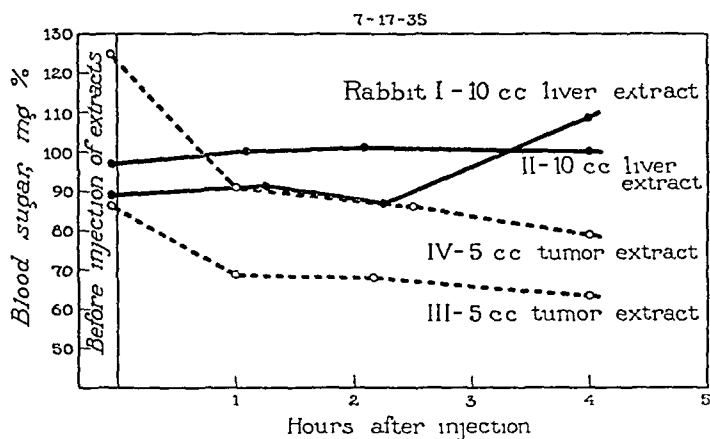


Fig 2—First assay of the extracts

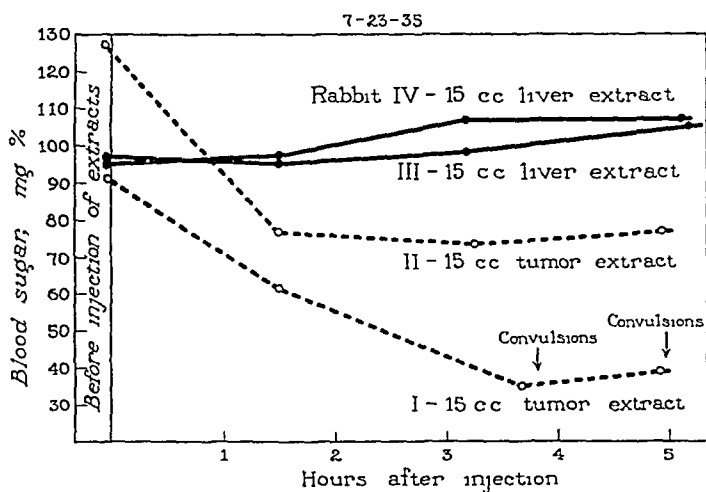


Fig 3—Second assay of the extracts

values, the value for blood sugar was lowered significantly for each of the four rabbits after the injection of the tumor extract, and in rabbit 1 typical convulsions ensued. This animal recovered completely when a solution containing 2 Gm. of dextrose was injected subcutaneously after a second series of convulsions. The evidence, therefore, for the presence of an insulin-like substance in the extract of the tumor nodules of the liver may be taken as conclusive.

The recovery of a blood sugar-lowering substance from the metastatic tumors of the liver thus confirms the microscopic evidence for the presence of islands of Langerhans in the tumors and demonstrates the capacity of these islands to function. Conversely, the failure of Best, Jephcott and Scott to obtain extracts capable of lowering the blood sugar level from any tissue except the pancreas justifies the view that the active substance in our extract of tumor tissue was actually insulin. Although the data are not extensive enough to warrant quantitative calculation of the amount of insulin present, the estimate of about 2.5 units for each 15 cc of extract seems conservative. On this basis the metastatic tumor tissue yielded, under the conditions of these experiments, around 260 clinical units of insulin per kilogram.

COMMENT

The hypoglycemic condition in this case seems clearly established as attributable to true "hyperinsulinism." The liver was extensively invaded by cancerous growth, yet at least a third of the organ was normal hepatic tissue, the function of this tissue was normal, as judged by the various tests of liver function. Moreover, ample stores of glycogen were present as indicated by microscopic examination of the tissue, and could be mobilized, as indicated by the increase in blood sugar content, when epinephrine was administered. Loss of hepatic function in respect to the storage and mobilization of glycogen, which may be postulated in the cases of primary cancer of the liver with hypoglycemia reported by Nadler and Wolfer,¹⁴ Crawford¹⁵ and Beers and Morton¹⁶ and in the cases of extensive fatty infiltration reported by Judd, Kepler and Rynearson,¹⁷ may therefore be excluded. As to possible dysfunction of the adrenal glands, there had not been symptoms of adrenal insufficiency during life, and at necropsy the adrenal glands were perfectly normal morphologically. The other glands of internal secretion (the pituitary body was not examined) likewise appeared normal on microscopic examination.

It may be emphasized again that the tissue extracted and shown to contain insulin, just as in the case of Wilder, Allan, Power and Robertson, was metastatic island cell carcinoma from the liver, not tissue taken

14 Nadler, W. H., and Wolfer, J. A. Hepatogenic Hypoglycemia Associated with Primary Liver Cell Carcinoma, *Arch. Int. Med.* **44**: 700-710 (Nov.) 1929.

15 Crawford, W. H. Hypoglycemia with Coma in a Case of Primary Carcinoma of the Liver, *Am. J. M. Sc.* **181**: 496-502 (April) 1931.

16 Beers, D. N., and Morton, J. J. Primary Carcinoma of the Liver with Hypoglycemia, *Am. J. Cancer* **24**: 51-55 (May) 1935.

17 Judd, E. S., Kepler, E. J., and Rynearson, E. H. Spontaneous Hypoglycemia. Report of Two Cases Associated with Fatty Metamorphosis of the Liver, *Am. J. Surg.* **24**: 345-363 (May) 1934.

directly from the pancreas. The quantity of insulin recovered in the extracts was rather small compared with the maximal yield from beef pancreas. In each instance, however, the tissues were frozen soon after death, thus inhibiting destruction of insulin, and the results obtained probably represent to a fair degree of accuracy the relative capacity of the metastatic tissue to produce insulin as compared with normal pancreatic tissue. Considering the large amount of metastatic tissue and the fact that its secretion, being released from neurogenic control, was probably continuous, there can be little doubt that the metastatic tumors may be held accountable for the hypoglycemia observed in this case and that this was a case of true hyperinsulinism.

The question as to whether malignant growths in general may contain extractable insulin-like substances deserves consideration. The literature on this subject up to 1927 (Wilder and others²) indicated that in all probability such is not the case, although there was one report to the effect that small amounts of insulin had been obtained from spindle cell sarcomas of rats (Roffo and Correa¹⁸). If at that time the criteria for proof of insulin activity, since enunciated by Best, Jephcott and Scott,¹² had been applied, it is possible that the outcome of the insulin assays might have been considered questionable. In the meantime the malignant tissue in two cases of primary carcinoma of the liver with hypoglycemia, those of Nadler and Wolfer¹⁴ and Beers and Morison,¹⁶ has been tested for the presence of insulin. The extracts were found to be inactive, whereas simultaneously prepared extracts of the pancreas, which was normal in both cases, contained insulin equivalent to a yield of about 100 units per kilogram. Although the patients in these two cases, and in a similar one described by Crawford,¹⁵ required enormous amounts of carbohydrate to maintain a normal level for blood sugar, it does not seem probable that production of insulin was responsible for the hypoglycemia. Nadler and Wolfer stated, in addition, that the cancer cells in their case possessed none of the characteristics of islet cells.

SUMMARY AND CONCLUSIONS

A case of spontaneous hypoglycemia is described in which frequent feedings of carbohydrate were required to avert convulsions and coma. The liver appeared to function normally and to be able to release glycogen as dextrose when epinephrine was injected. At necropsy carcinoma of the islands of Langerhans was present, with multiple metastases, particularly to the liver. The cells of the metastatic nodules

18 Roffo, A. H. and Correa, L. M. Presence in Malignant Growths of a Substance Resembling Insulin, *Prensa med. argent.* **13** 668-669 (Dec. 20) 1926 abstr., *J. A. M. A.* **88** 767 (March 5) 1927.

in the liver closely resembled those of normal islands of Langerhans. This view was confirmed by the preparation from the hepatic nodules of an extract which contained insulin, a substance which, according to available evidence, is present in extractable amounts solely in cells of the islands of Langerhans. Classification of the condition as due to true hyperinsulinism seems justified.

This is the second case in which the presence of insulin in metastatic carcinoma of the islands of Langerhans has been demonstrated. The previous demonstration of this during study of a similar case by Wilder, Allan, Power and Robertson is fully confirmed, and the evidence is thus materially strengthened that metastatic carcinoma cells of the islands of Langerhans can retain the function of the parent cells.

MEDICINAL TREATMENT OF ANGINA PECTORIS

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Accurate evaluation of the efficacy of therapy in angina pectoris is difficult, for since cardiac pain is a subjective sensation with no constant outward manifestations, it is necessary to rely almost wholly on the patient's description of his symptoms. Variations in the physical and emotional activity of daily life, changes in the prevailing temperature and other factors difficult to evaluate cause changes in the frequency and severity of attacks of angina and make conclusions regarding therapeutic measures uncertain.

In a previous communication¹ it was shown that under standardized conditions a definite measurable amount of exercise will always induce a typical attack of angina in a given patient. This "standardized exercise tolerance test" has been used to measure objectively the therapeutic benefit derived from procedures such as total thyroidectomy² and to measure the heart rate and blood pressure during attacks of angina³. The present communication deals with its use in judging the therapeutic benefit derived from medicinal agents.

PLAN OF INVESTIGATION

Selection of Patients—The subjects with angina pectoris selected for this study had symptoms corresponding to the syndrome described by Heberden⁴. All were ambulatory and, so far as could be determined, suffered from no illness other than

This investigation was aided by a grant from the DeLamar Mobile Research Fund.

From the Medical Research Laboratories of the Beth Israel Hospital and the Department of Medicine of the Harvard Medical School.

1 Riseman, J E F, and Stern, B. A Standardized Exercise Tolerance Test for Patients with Angina Pectoris on Exercise, *Am J M Sc* **188** 646, 1934.

2 Blumgart, H L, Riseman, J E F, Davis, D, and Berlin, D D. Therapeutic Effect of Total Ablation of Normal Thyroid on Congestive Heart Failure and Angina Pectoris. III. Early Results in Various Types of Cardiovascular Disease and Coincident Pathologic States Without Clinical or Pathologic Evidence of Thyroid Toxicity, *Arch Int Med* **52** 165 (Aug) 1933.

3 Riseman, J E F. The Relationship of the Systolic Blood Pressure and Heart Rate to Attacks of Angina Pectoris on Exercise, *Am Heart J* **12** 53, 1936.

4 Heberden, W. Commentaries, *M Tr Coll Physicians*, London **2** 59, 1768.

disease of the coronary arteries. Patients with financial, domestic or social difficulties which were important factors in precipitating attacks were not included in this series. No patient was accepted for treatment who had experienced coronary occlusion within six months, and no patient was included in the final series unless his reaction to at least five different drugs had been studied. The periods of observation ranged from three to thirty-six months.

Of the twenty-six patients studied, twenty-one were men and five women. One patient was 38, four patients were from 47 to 49, sixteen were from 50 to 59, four were from 60 to 66 and 1 patient was 72 years of age. Thirteen had hypertension (a systolic blood pressure of 160 mm of mercury or higher or a diastolic blood pressure of 100 mm or higher). Roentgenograms taken at a distance of 7 feet (215 cm) showed an enlarged cardiac shadow in eight patients. Electrocardiographic tracings showed changes consistent with disease of the coronary arteries in fifteen.

No attempt was made to alter the patients' mode of living in any way. Eight patients were unable to work because of their illness, fourteen were able to perform light work or housework in spite of attacks of pain and the remaining four worked full time.

All twenty-six patients experienced angina on exertion, this was confirmed by observation under standard conditions. Twenty gave a history of attacks also under emotional stress, eight experienced paroxysms also while at rest and seven occasionally had pain during sleep. The frequency of attacks under ordinary conditions of daily life varied considerably. One patient suffered from fifty to one hundred attacks every week, eleven patients stated that occasionally a week or ten days would elapse without cardiac pain while the remaining fourteen patients usually had at least one attack every day.

Method of Study—To evaluate the severity of the condition and to obtain specific criteria by which to gage the results of therapy, all patients were observed in a special clinic for from one month to one year before therapy was begun. Fifteen different drugs were used, and the effect of mixed therapy also was studied. Each drug was used by at least twenty different patients. The order of administration was different for each patient. The medicines were taken by mouth three or four times daily on arising, after lunch, after the evening meal and (when given four times daily) before retiring. Glyceryl trimtrate, for reasons to be explained later, was given at hourly intervals throughout the day. The doses of digitalis were calculated so that the patient would receive his full requirement of digitalis (according to weight by the method of Eggleston⁵) in seven days. The doses of drugs other than digitalis were the same for all patients, being sufficiently large to be therapeutically effective without a high incidence of untoward results.

Each drug was administered for at least one week before an attempt was made to evaluate the results. Two observers independently examined each patient, one using the usual clinical methods and the other the standardized exercise tolerance test. The results were compared only after each observer had independently reached a decision regarding the effect of the drug.

When there was evidence that a drug had exerted a beneficial effect, the medication was discontinued, and an inert tablet of similar appearance was substituted. When the cardiac symptoms had returned to their usual severity, as judged by clinical criteria and by the exercise tolerance test, other drugs were tested, and

5 Eggleston, C. Administration of Digitalis by the "Eggleston Method," J. A. M. A. **74** 733 (March 13) 1920.

at a later date the medication which had yielded a beneficial result was again administered, this time in a disguised form (sugar coated, in capsule or painted with tincture of cudbear)

Evaluation of the Results—The effect of medication was judged clinically according to three criteria (1) the patient's own estimation of the efficiency of the drug, (2) the actual number of attacks experienced or the actual number of tablets of glyceryl trinitrate required during the period of medication and (3) the occurrence of untoward or unexpected symptoms. The number of attacks experienced during the period of medication was compared with the clinical condition before therapy was started and with that of the period when inert medication was given. The physical and emotional activity during this period also was estimated and was taken into consideration when necessary in evaluating the results.

Objective evaluation of the results of therapy was obtained by the standardized exercise tolerance test¹. The test was performed in a room in which the temperature was maintained between 45 and 55 F. All tests were performed at least one hour after a light breakfast was eaten and from one and one-half to two and one-half hours after medication was received. In several instances tests were performed at different intervals after the drug was taken, in order to determine how soon it began to act and how long the action continued. Only one test was performed on a single day, and no test was performed if the patient had experienced an attack within one hour prior to his appearance at the clinic. The exercise consisted of repeatedly mounting and descending a two step staircase until precordial pain or discomfort developed. No untoward effects were experienced from this task, the angina subsided shortly after the work was stopped and in no instance was the precordial pain more severe than that experienced in daily life. No attempt was made to influence the rate of exercise, since patients will perform customary exertion, such as climbing stairs, at a fairly constant rate, and any attempt to influence the rate of exertion is usually followed by a change in exercise tolerance¹. The exercise tolerance, according to this method is the number of trips required to induce a typical attack of anginal pain. A single trip consists of one ascent and one descent of the staircase. The exercise tolerance of each patient was determined by at least three tests before medication was begun.

Under these constant conditions of exercise, temperature, food and emotional state, patients with angina have typical attacks after fixed amounts of exercise, even though intervals of several months separate the tests. This is shown by experience in over fifteen hundred tests performed by over one hundred and fifty patients⁶.

RESULTS

Results Based on Clinical Evaluation Alone—According to the patients' reports, lactose or sodium bicarbonate was beneficial as frequently as other drugs (chart 1). Close questioning, however, frequently revealed that essentially the same number of attacks was experienced during any given period. The improvement apparently consisted of a sense of well-being, induced not by specific medication but by the fact that medical supervision was being given. Nine of twenty-one patients felt that they had been helped by the first few medications. Several felt better with every drug administered.

⁶ Riseman, J. E. F., and Brown, M. G. Unpublished data.

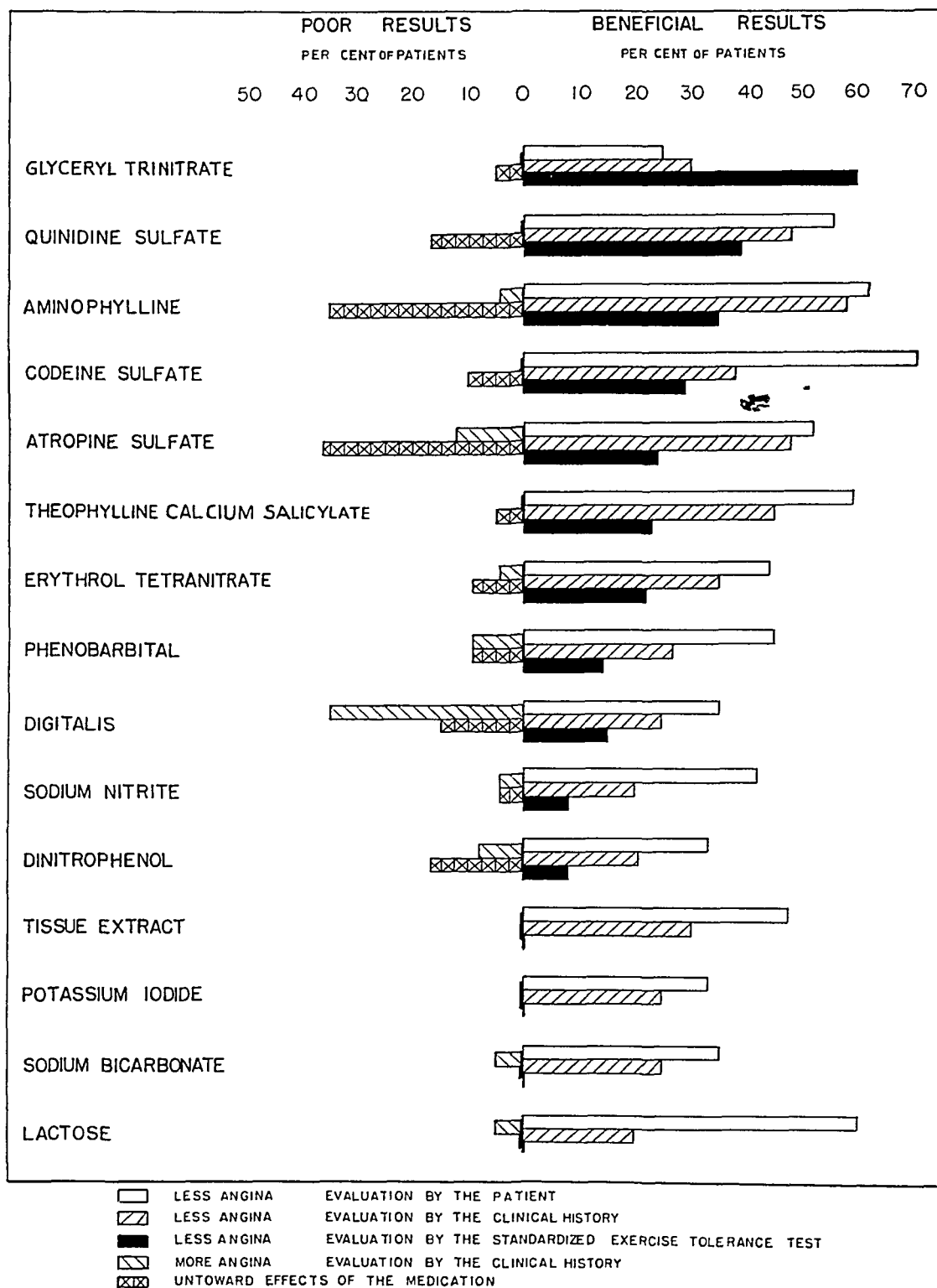


Chart 1—The frequency of response of angina pectoris to medicinal treatment.

Determination of the actual number of attacks experienced during a given period of medication (or determination of the number of glyceryl trinitrate tablets used) suggested that sodium bicarbonate and lactose pills were of benefit in about a fifth of the patients, whereas aminophylline, quinidine sulfate and atropine sulfate helped approximately half the patients (chart 1). The clinical histories revealed that many patients, even without medication, occasionally experienced intervals of a week or more when they were comparatively free from cardiac pain. Furthermore, during periods of unemployment or warm weather a diminution in the frequency of attacks often occurred. Under such conditions it is obviously impossible to estimate how much of the apparent improvement was due to medication.

Results Based on the Standardized Exercise Tolerance Test Alone—No patient was able to perform more work after taking lactose or sodium bicarbonate, furthermore, when some other medicine had been of benefit, the improvement always disappeared when the patient was given one of these two drugs. When the administration of a drug resulted in an increased ability to work, repetition of the period of medication practically always resulted in the same increase in exercise tolerance. With few exceptions, patients who showed an increase in exercise tolerance of at least 20 per cent experienced a diminution in the frequency of attacks in daily life. It is evident that clinical evaluation alone indicated improvement more frequently than actually occurred. The standardized exercise tolerance test, therefore, serves as a valuable check on the efficacy of therapy.

Evaluation of Results by Both the Clinical History and the Exercise Tolerance Test—Improvement due to medication indicates that the patient reported he had been benefited by the drug, there was a decrease in the frequency of attacks in daily life and there was a definite increase in exercise tolerance. Furthermore, these indications of improvement disappeared when inert medication was given and reappeared in the same degree each time the specific medication was readministered.

The different drugs varied in their efficacy, and the different patients varied in their reaction to medication. Nine of the twenty-six patients (35 per cent) were not helped by any of fifteen different drugs. One patient responded to eight different medicines, fifteen were helped by from two to six drugs while the remaining patient responded to one of five drugs.

Inert Medication (pink lactose tablets four times daily, tablets of sodium bicarbonate, 5 or 10 grains [0.3 to 0.65 Gm.] three or four times daily)—Each of these two different types of inert medicament was given to twenty different patients. Seven patients believed that they were helped by sodium bicarbonate, five reported a diminution in the fre-

quency of attacks (chart 1) Twelve believed that the lactose tablets had been of value four of these reporting that they had less pain while taking the tablets (chart 1) In no instance was the use of either of these drugs attended by an observable ability to perform an increased amount of work (charts 1 and 2)

Five patients believed the inert medicament had made them worse, however, the exercise tolerance remained unchanged, and the history revealed that they had had similarly poor weeks before medication was started The increase in symptoms was probably due to contrast, for the inert drug was given after the use of beneficial medicament Neither

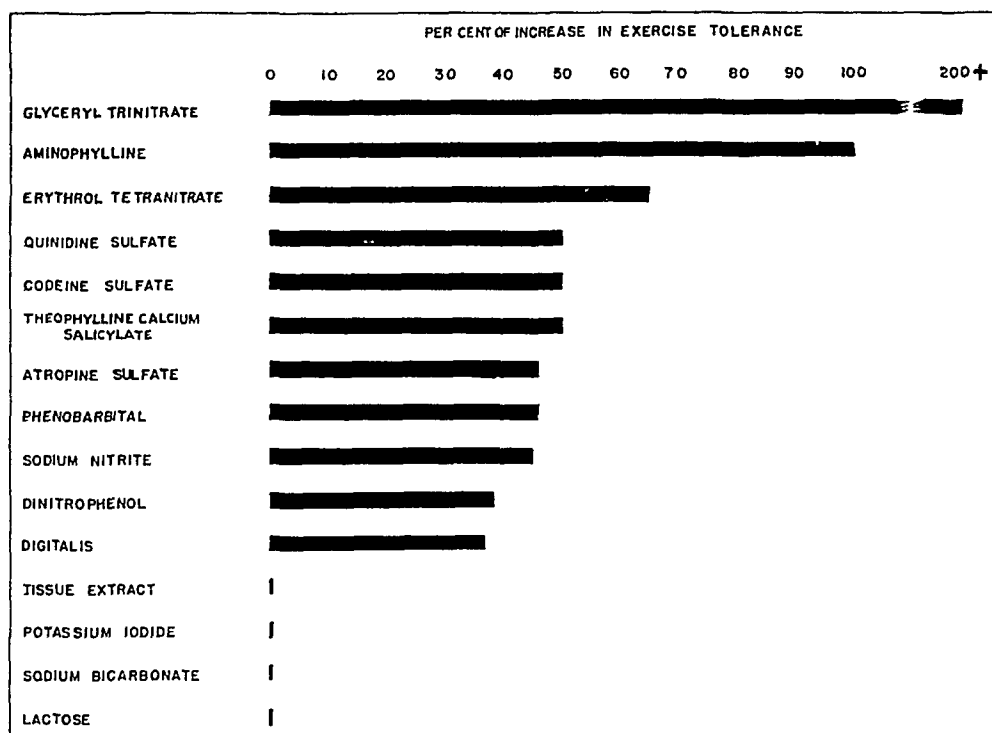


Chart 2—The increase in the amount of work possible without pain after medicinal therapy

sodium bicarbonate nor lactose was followed by any untoward symptoms, although one patient complained of cough and another of headache, which they attributed to the medication

Potassium Iodide (10 grains [0.65 Gm] three times daily) and *Tissue Extract* (1 tablet orally three times daily for at least three weeks) — The results with these drugs were similar to those obtained with lactose and sodium bicarbonate (charts 1 and 2) Potassium iodide was used by twenty-four and tissue extract by twenty patients One patient had no attacks clinically during the three weeks that he took tissue extract, and his exercise tolerance increased from thirty-five to seventy-six trips Repetition of the medication on two other occasions failed to show any

improvement, the first result in all probability was due to spontaneous variation in the course of the disease

No untoward effects were observed in patients who took tissue extract. One patient showed marked swelling of the submaxillary glands every time potassium iodide was administered

Glyceryl Trinitrate (1/500, 1/200 and 1/100 grain [0.1, 0.3 and 0.6 mg] at intervals throughout the day) —In order to determine the duration of action of this drug the exercise tolerance was determined at varying intervals after a tablet of glyceryl trinitrate had been placed under the tongue. Especially prepared tablets containing 1/500 grain (0.1 mg) of glyceryl trinitrate were employed, and the results were checked by the use of stronger doses. Only one of twenty patients experienced slight flushing and a slightly uncomfortable sense of fullness

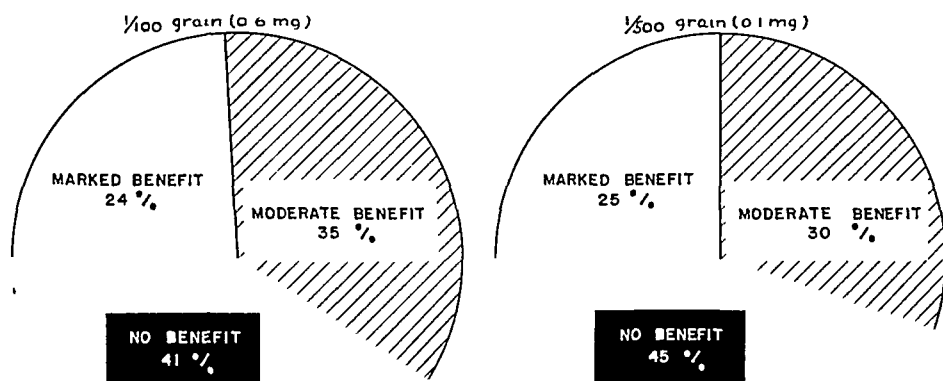


Chart 3—The proportion of patients helped by glyceryl trinitrate given to prevent angina. The increase in exercise tolerance is shown as follows. The white area indicates 100 + per cent for thirty minutes, the shaded area, 100 per cent for from five to fifteen minutes, and the black area, no increase.

in the head after taking the smaller dose, whereas eleven of seventeen patients who received 1/100 grain (0.6 mg) of glyceryl trinitrate complained of severe headache or other unpleasant symptoms.

The maximum prophylactic effect was evident about two minutes after the drug was taken. The duration and the degree of therapeutic effect varied in the twenty patients studied (chart 3). Five patients who without medication had angina after approximately thirty-five trips were able to undertake as many as one hundred trips without pain two minutes after taking 1/500 grain (0.1 mg) of glyceryl trinitrate. This effect continued for approximately ten or fifteen minutes and then gradually diminished but did not disappear entirely for from thirty to sixty minutes. The therapeutic effect of 1/100 grain (0.6 mg) of glyceryl trinitrate was even more prolonged—as long as seventy-five

minutes in one case (chart 4) Four of these five patients were completely free from anginal attacks in daily life when they took 1/500 grain (0.1 mg) of glyceryl trinitrate at hourly intervals throughout the day One of these patients was able to perform heavy work in a shipyard The fifth patient was the one who was made slightly uncomfortable by even 1/500 grain (0.1 mg), and it was inadvisable to use it clinically

Six patients showed a moderately favorable response After taking 1/500 grain (0.1 mg) of glyceryl trinitrate they could do approximately twice as much work, and the attacks were of shorter duration and less severe Five or ten minutes after the drug was taken, however, the exercise tolerance was the same as before (chart 5) These patients

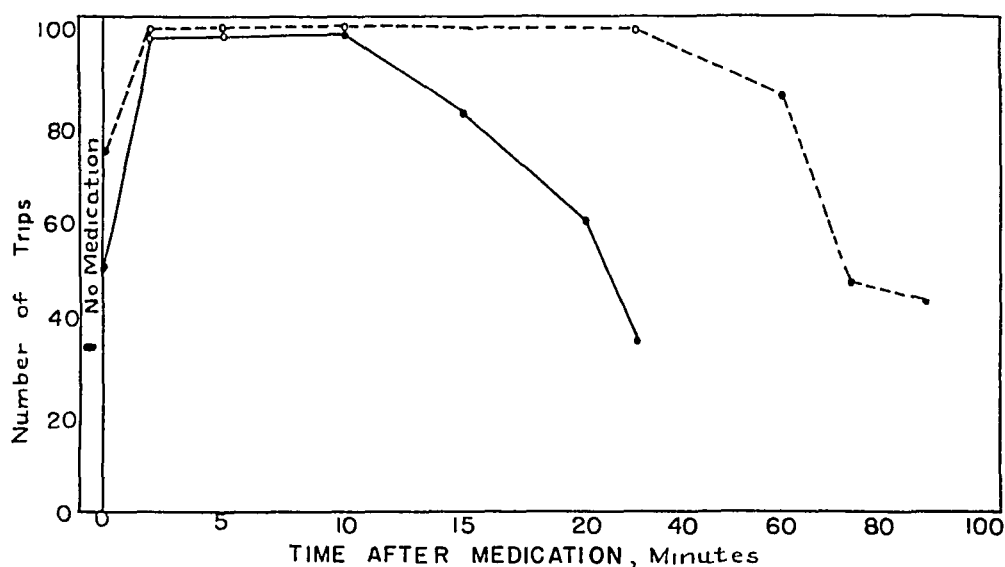


Chart 4—The exercise tolerance of patient M. L. at different intervals after taking glyceryl trinitrate (only one test was performed on a given day) This patient showed a marked response to the drug In charts 4 to 6 a black circle indicates an anginal attack, a white circle, no attack, a solid line, 1/500 grain (0.1 mg) of glyceryl trinitrate, and a dash line, 1/100 grain (0.6 mg) of glyceryl trinitrate

secured considerable relief from pain by taking 1/500 grain before going out into the cold or before undertaking undue exertion This protection was of relatively short duration, and administration of the drug at hourly intervals did not render the patients completely free from attacks in daily life The effect of 1/100 grain (0.6 mg) was more lasting (about five minutes longer), but for all practical purposes the smaller doses were equally satisfactory

In the remaining nine patients the ability to perform work was not influenced by glyceryl trinitrate (chart 6), and these persons observed no changes in their clinical condition when taking glyceryl trinitrate throughout the day or before performing any unusual exercise

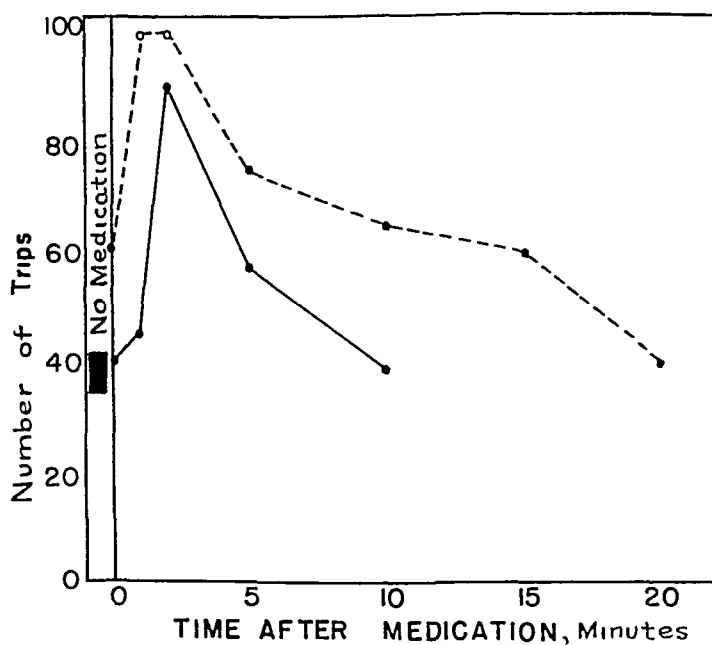


Chart 5—The exercise tolerance of patient E. Ar. at different intervals after taking glyceryl trinitrate (only one test was performed on a given day) This patient showed a moderate response to the drug

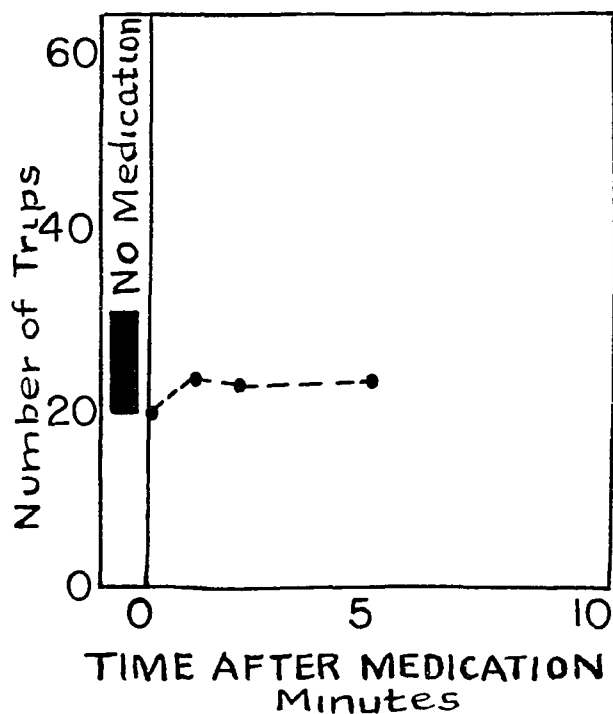


Chart 6—The exercise tolerance of patient L. C. at different intervals after taking glyceryl trinitrate (only one test was performed on a given day) This patient showed no response to the drug

Aminophylline (3 grains [0.2 Gm.] four times daily) —This drug was used by all twenty-six patients, nine of whom showed clinical improvement and an increased ability to work (chart 1). The increase in exercise tolerance following the use of this drug varied from 24 to 100 per cent (chart 2). Three other patients showed a 13 to 17 per cent increase in exercise tolerance but no change in clinical frequency of attacks.

Nine of the twenty-six patients had nausea or gastric distress when taking 3 grains (0.2 Gm.) of aminophylline (chart 1). In only one instance was this so severe that the medication had to be discontinued, in other instances the distress could be decreased by giving the pills together with sodium bicarbonate. Smaller doses (1½ grains [0.1 Gm.] three or four times daily) gave less gastric discomfort but failed to give satisfactory therapeutic benefit.

Quinidine Sulfate (5 grains [0.3 Gm.] four times daily) —Nine of twenty-three patients showed an increase in exercise tolerance of from 23 to 50 per cent (chart 2) after taking this medicament (chart 1). Three other patients showed from 14 to 19 per cent increase but no satisfactory clinical response. Three patients who failed to show any response to other medication did not receive quinidine.

Slight untoward effects were experienced by four patients. In one patient dermatitis developed and disappeared when the drug was withdrawn. The other three complained of diarrhea, which diminished when the dose of the drug was decreased to 3 grains (0.2 Gm.) four times daily, the therapeutic effect also was lessened with the smaller dose.

Atropine Sulfate (1/120 grain [0.5 mg.] four times daily) —Administration of this drug was followed in six of twenty-five cases by an increased ability to work (chart 1). The increase in exercise tolerance varied from 25 to 46 per cent (chart 2). Four of these patients showed a satisfactory clinical response, and one was helped by this medicament but not by quinidine or aminophylline. After the use of atropine one patient had a complete remission of symptoms both by clinical history and by exercise tolerance test on three distinct occasions separated by intervals of several months, the duration of the remission was at least two months. This patient showed a striking response to other drugs also, especially phenobarbital.

Unpleasant effects, especially dryness of the mouth, were experienced by nine patients (chart 1), in most instances the discomfort was severe. Several patients experienced more attacks while taking atropine (chart 1), possibly because of the discomfort caused by the drug. Two patients refused to continue the medication.

Three patients who experienced no relief from oral therapy were given the drug hypodermically in order to assure absorption. The

exercise tolerance was determined shortly thereafter, when signs of the effect of atropine, such as dryness of the mouth and blurring of vision, were evident. On successive days the dose was increased gradually from 1/120 to 1/60 grain (0.5 to 1.1 mg). No change in exercise tolerance ensued.

Digitalis—Twenty patients were given sufficient digitalis in the course of a week to approximate their full requirements. Three patients showed a slight but definite increase in ability to perform work (22 to 33 per cent increase in exercise tolerance) and a definite diminution in the frequency of attacks during daily life (charts 1 and 2). These patients were benefited by aminophylline also.

TABLE 1—*Summary of Results Obtained in the Treatment of Angina Pectoris with Codeine Sulfate, Theophylline Calcium Salicylate, Erythrol Tetranitrate, Phenobarbital, Sodium Nitrite and Dimitrophenol*

	Number of Patients Studied	Patients Improved		Unpleasant or Toxic Effects	
		Number	Percentage	Number of Patients	Symptoms
Codeine sulfate, $\frac{1}{2}$ grain (0.03 Gm.) four times daily	21	6	26	2	Obstipation
Theophylline calcium salicylate, 4 grains (0.26 Gm.) four times daily	22	5	23	1	Moderate gastric distress
Erythrol tetranitrate, $\frac{1}{4}$ grain (0.016 Gm.)* four times daily	23	5	22	2	Headache
Phenobarbital, $\frac{1}{2}$ grain (0.03 Gm.) four times daily	22	3	14	2	Drowsiness
Sodium nitrite, 1 grain (0.065 Gm.) four times daily	26	2	8	1	Slight headache
Dimitrophenol, $\frac{5}{12}$ grain (0.027 Gm.) four times daily	24	2	8	3	Nausea, tinnitus, loss of weight

* Larger doses were tried but had to be discontinued because of severe headaches.

The most striking effect of digitalis was an increase in the frequency and severity of the attacks of cardiac pain in daily life in seven patients, five of whom showed almost continuous angina (chart 1). The attacks became so frequent and so severe that it was deemed inadvisable to determine the exercise tolerance except for one patient, who showed a decrease of 21 per cent.

Other Substances—The results obtained with codeine sulfate, theophylline calcium salicylate, erythrol tetranitrate, phenobarbital, sodium nitrite and dimitrophenol are summarized in table 1 and charts 1 and 2. No further comment is needed at this point.

COMMENT

Evaluation of Methods—The clinical history elicits information as to the number and frequency of attacks experienced under the conditions of daily life and the patient's impression regarding the efficacy of treat-

ment The exercise tolerance test measures under controlled conditions the effect of the drug in preventing the onset of an attack and indicates the rôle played by medication in bringing about improvement It is necessary to combine the information obtained from both these sources in order to obtain an accurate picture of the response to therapy

The unchecked clinical evaluation indicates that excellent results can be obtained in some cases from any form of medicinal therapy, including drugs which are inert Evans and Hoyle⁷ found that "a measure of improvement appears to result from every remedy tried, and at least as great an improvement during treatment with placebo" The experience of Master⁸ and our own results judged solely on clinical data agree closely with those of the English investigators This apparent improvement is probably due in large measure to the alleviation of anxiety The problem is complicated further by the inability of the patient and doctor to differentiate between actual improvement brought about by medication and a decrease in symptoms due to variations in daily activity or spontaneous variations in the natural history of the disease

If medication induces improvement in a patient who has attacks on exertion, this improvement should be evidenced by an ability to perform more work than was possible without medication

The standardized exercise tolerance test duplicates the stimuli and environment which precipitate the majority of attacks in daily life, and, as far as can be determined, the attacks induced are similar to those experienced in normal life In the absence of medication the amount of work which patients can perform before pain develops is extraordinarily constant under the standardized conditions employed in this study Any change in exercise tolerance which regularly appeared after a given medication and which disappeared when the medication was omitted must have been caused by the drug

An increase in exercise tolerance was rarely observed without clinical improvement When the patient was able to exercise to the point of fatigue without pain, attacks in daily life were generally absent Likewise, when an increased tolerance to exercise of from 50 to 75 per cent was present, the patient usually experienced fewer attacks When an increase in exercise tolerance of less than 20 per cent was present, any apparent improvement was probably not related to treatment

In order to make the results of this investigation directly applicable to the treatment of patients with angina in clinical practice, the method

7 Evans, W., and Hoyle, C. The Comparative Value of Drugs Used in the Continuous Treatment of Angina Pectoris, *Quart J Med* **2** 311, 1933

8 Master, A. M. Treatment of Coronary Thrombosis and Angina Pectoris, *M Clin North America* **19** 873, 1935

of administering the drugs has been similar to that employed in general practice. No attempt has been made in this study to determine the influence of prolonged medicinal therapy. The course of the disease is so variable over long periods that it is almost impossible to differentiate between improvement due to prolonged therapy and spontaneous improvement brought about by time.

Value of Medication—The doses of lactose and sodium bicarbonate used in these studies could not conceivably have had any direct influence on cardiac pain. The excellent clinical results obtained with these inert drugs, by others⁹ as well as by ourselves, should make one skeptical of therapeutic claims based on clinical evaluation alone.

Potassium iodide has been used for generations in a number of different conditions. While of undoubted value in the treatment of cardiac pain due to syphilitic heart disease, it evidently has no place in the treatment of Heberden's angina.

Tissue extract is a more recent addition to medicine. Rumors as to its clinical effectiveness in angina have been frequent since its introduction by Schwartzman¹⁰ in 1929. We have found no objective evidence that tissue extract administered orally is of value in treating cardiac pain.

The use of glyceryl trinitrate to decrease the duration of an attack is well recognized. The prophylactic value of the drug has received insufficient attention. Muriell's¹¹ original communication advocated the administration of glyceryl trinitrate several times a day in order to prevent attacks. More recently it has been suggested that it be used immediately before exertion is undertaken.¹² The present communication offers objective illustration of the value of these methods.

Approximately one third of the patients can be rendered completely free from attacks by taking 1/500 grain (0.1 mg.) of glyceryl trinitrate under the tongue at hourly intervals during the day. In approximately another third the beneficial effect is of only a few minutes' duration, such patients can secure considerable temporary relief by using the drug before any undue exertion or emotional strain. The remaining group of patients show no increase in ability to perform work after taking glyceryl trinitrate, or in fact any drug. It is important to realize that for all practical purposes small doses (1/500 grain) are as effective in preventing attacks as are larger doses and are attended by much less risk of inducing uncomfortable or harmful side-reactions.

9 Evans and Hoyle⁷ Master⁸

10 Schwartzman, M. S. Ein neuer Weg in der Therapie der Angina pectoris, München med Wchnschr **76** 1329, 1929

11 Murrell, W. Nitroglycerine as a Remedy for Angina Pectoris, Lancet **1** 80, 1879

12 White, P. D. Heart Disease, New York, The Macmillan Company, 1931

Aminophylline was introduced by Dessauer¹³ as a readily soluble preparation of theophylline. Musser¹⁴ and Gilbert and Keir¹⁵ have advocated its use in angina pectoris. When used in adequate doses the drug is frequently of undoubted benefit. It should be emphasized that a dose of less than 3 grams (0.2 Gm.) is of little value. The untoward effects in our experience are slight and offer little drawback to its clinical use.

The use of quinidine sulfate in the treatment of angina pectoris was recommended by Proger, Minnich and Magendantz.¹⁶ These authors said they felt that it was of value for those patients whose heart rate failed to increase sufficiently during exercise or who showed extra systoles on exertion. Wayne and Graybiel¹⁷ used the drug with success for a patient with ventricular fibrillation and angina sine dolore. We have found no correlation between the efficacy of quinidine sulfate in angina pectoris and the heart rate or rhythm during exertion. Furthermore, quinidine has been of distinct value for patients who have cardiac pain while at rest or when in bed.

Our use of quinidine sulfate was attended by no significant untoward effects; it is realized, however, that an occasional patient may be hypersensitive or show an idiosyncrasy to this drug.

Nine patients were given aminophylline and quinidine sulfate simultaneously (table 2). The combination was rarely of greater value than either drug given alone.

Codeine sulfate is clearly of value in the treatment of cardiac pain, but like other opium derivatives it is unsuited for prolonged use. If the relief which narcotics afford were caused by the analgesic action alone, it would be possible theoretically for a patient to continue exercising without pain until other, more serious consequences of myocardial anoxemia developed. The duration, severity and other characteristics of the attacks experienced after codeine sulfate was administered differed in no way from those when the patient was not taking the medicament, and there were no untoward effects. Possibly codeine acts to depress the patient's sensitivity to emotional reactions in general, thus

13 Dessauer, P. Euphyllin, ein neues Diuretikum, *Therap. Monatschr.* **22** 401, 1908.

14 Musser, J. H. Theophylline-Ethylenediamine in Heart Disease Associated with Pam, *J. A. M. A.* **91** 1242 (Oct. 27) 1928.

15 Gilbert, N. C., and Kerr, J. A. Clinical Results in Treatment of Angina Pectoris with Purine Base Diuretics, *J. A. M. A.* **92** 201 (Jan. 19) 1929.

16 Proger, S. H., Minnich, W. R., and Magendantz, H. The Circulatory Response to Exercise in Patients with Angina Pectoris, *Am. Heart J.* **10** 511, 1935.

17 Wayne, E. J., and Graybiel, A. Observations on the Effect of Food, Gastric Distension, External Temperature, and Repeated Exercise on Angina of Effort, with a Note on Angina Sine Dolore, *Clin. Sc.* **1** 287, 1934.

eliminating one stimulus which might induce pain or make it more easy for attacks to be produced by other stimuli, such as exertion

Physicians frequently prescribe phenobarbital, yet there is little evidence that this drug causes an actual decrease in cardiac pain. Nine of twenty-two patients, however, volunteered the information that they experienced a sense of well-being while taking phenobarbital entirely different from that noted with any other form of medication. As one patient expressed it, "It made the pain easier to bear."

Phenobarbital, like codeine, probably renders the patient less sensitive to emotional stimuli and may also lessen the rate at which exercise is undertaken in daily life. This is illustrated by one patient who showed striking clinical improvement and was able to perform more work before pain developed after having secured a good night's sleep with the aid

TABLE 2—*Comparison of the Exercise Tolerance After Aminophylline, Quinidine Sulfate and a Combination of the Two Drugs*

Patient	No. of Trips			
	No Medication	Aminophylline*	Quinidine Sulfate†	Aminophylline* and Quinidine Sulfate†
D. C.	20/32	29	23	23
P. R.	26/40	23	18	18
Y. E.	12/23	16	30†	33†
H. Sr.	26/31	22	38	34
H. S.	30/44	54	66†	64
M. L.	33/34	57	34	50
E. A.	34/42	35	50	48
B. L.	8/11	10	10	16
S. R.	31/40	44	40	60

* Three grains (0.2 Gm.) four times daily

† Five grains (0.3 Gm.) four times daily

‡ No attack was induced by exercise

of a single dose of $1\frac{1}{2}$ grains (0.1 Gm.) of phenobarbital before retiring. The comforting effect of a good night's sleep apparently rendered this patient less sensitive to other stimuli during the day and so freed him from pain to a considerable degree. The effect of combining sedatives with other drugs deserves further study.

It has been stated that atropine prevents angina,¹⁸ makes it worse¹⁹ and has no effect on the condition.²⁰ The present investigation shows that different patients react differently to the drug. It is apparently of

18 Allbutt, T. C. *Diseases of the Arteries, Including Angina Pectoris*, London, Macmillan & Company, 1915. Goldhammer, S., and Scherf, D. *Elektrokardiographische Untersuchungen bei Kranken mit Angina pectoris ("ambulatorischer" Typus)*, *Ztschr. f. klin. Med.* **122**: 134, 1932.

19 (a) Scherf, D., and Schnabel, P. *Atropine bei Angina pectoris*, *Klin. Wchnschr.* **13**: 1397, 1934. (b) Wayne, E. T., and Laplace, L. B. *Observations on Angina of Effort*, *Clin. Sc.* **1**: 103, 1933.

20 Stevens, A. A. *Angina Pectoris and Allied Conditions*, *M. Clin. North America* **1**: 293, 1917.

clinical value in about one third of the cases. Unfortunately one cannot predict which patient will be helped by the drug. The clinical value is further diminished by the high frequency of unpleasant reactions. In order to obviate these untoward symptoms, two synthetic preparations (syntiopan and novatropine) were used by three patients who were helped by atropine. No untoward effects were noted, but neither of these commercial preparations had the slightest beneficial effect on cardiac pain.

Coogan²¹ had used theophylline calcium salicylate with good clinical response in six cases of angina. The two purine derivatives used in this study had approximately the same theophylline content, nevertheless, aminophylline afforded relief to a greater number of patients and to a greater degree. An occasional patient, however, responded to the calcium salt and not to the ethylene diamine mixture. There is some evidence⁶ that a double dose (2 tablets four times daily) of theophylline calcium salicylate is of greater value than the single dose, however, the cost of the drug at the present time practically prohibits such use. Theophylline calcium salicylate caused less gastric distress, but the dose of aminophylline used did not cause sufficient discomfort to prevent its use in angina. The reasons for these differences in action are not clear at the present time.

Erythrol tetranitrate was introduced for the treatment of angina pectoris by Bradbury²². Both erythrol tetranitrate and aminophylline are vasodilators, and these drugs are effective for the same patients. Erythrol tetranitrate in small doses is less likely to be accompanied with untoward effects and may be more satisfactory for some patients.

The work of Gilbert and Fenn²³ indicated that digitalis decreases the coronary blood flow. These investigators found that this drug frequently caused an increase in the clinical frequency of attacks²⁴. The results of the present investigations are in complete accord with this view. This deleterious effect, however, does not occur in every instance, in fact, some patients are helped by the use of the drug. One would expect a decrease in angina in some patients who also show congestive failure, for in such cases the administration of digitalis should improve the general circulation, including that of the heart. Because of the strikingly bad effect in a large percentage of patients, this drug should be used with great caution in angina pectoris.

21 Coogan, T. J. Some Clinical Observations on the Uses of Theophylline Calcium Salicylate, *Tr. Am. Therap. Soc.* **34** 137, 1934.

22 Bradbury, T. B. Some New Vasodilators, *Brit. M. J.* **2** 1213, 1895.

23 Gilbert, N. C., and Fenn, G. K. Effect of Digitalis on the Coronary Flow, *Arch. Int. Med.* **50** 668 (Nov.) 1932.

24 Fenn, G. K., and Gilbert, N. C. Anginal Pain as a Result of Digitalis Administration, *J. A. M. A.* **98** 99 (Jan. 9) 1932.

In an occasional patient sodium nitrite may be of distinct value. One patient, not included in the present series, became completely free from attacks both clinically and by exercise tests on each of three occasions when the drug was given. The remission continued for several months after the drug was discontinued. Such responses, however, are rare, and despite reference²⁵ to the use of sodium nitrite in the treatment of angina there is little to indicate its use now that other more effective vasodilators are available.

Tainter and his co-workers²⁶ have reported disappearance of angina pectoris following the use of dinitrophenol. The optimum dose in our experience⁶ for patients with angina pectoris was 100 mg daily. In view of the frequency with which untoward effects were experienced with even such small doses, it appears inadvisable to use this drug in the treatment of cardiac pain.

The apparent clinical improvement which follows the use of any drug (including placebos) in angina pectoris led Evans and Hoyle⁷ to conclude "We have been unable to convince ourselves that any drug tested is worthy even of trial in the routine treatment of the disease." The work of Wayne and Laplace^{19b} and the results of the present investigation indicate that after the administration of certain drugs there is a distinct increase in the amount of work which can be performed by patients with angina pectoris. The present investigation also indicates that several of these drugs are of distinct value in the treatment of angina.

A few patients may be rendered completely free from cardiac pain under ordinary conditions of living as long as they continue taking effective medication. Occasionally these remissions continue after the medicine has been omitted, such occurrences, however, are comparatively rare. The majority of patients experience fewer attacks after effective medication but are not completely free from pain. About one-third derive no benefit from any of the customary forms of medicinal therapy.

We have no adequate means at the present time of predicting which drug will benefit a given patient, or, in fact, whether the patient will respond to any medication in any degree. In our experience a satisfactory method for medicinal treatment of patients with frequent attacks of angina pectoris has been to administer small doses of glyceryl trinitrate at hourly intervals throughout the day and before any undue exertion. Frequently it is of value to combine this therapy with phenobarbital or codeine. Patients whose attacks are less frequent also may

25 Evans, W., and Hoyle, C. The Prevention and Treatment of Individual Attacks of Angina Pectoris, *Quart J Med* **3** 105, 1934. Hay, M. Nitrite of Sodium in Treatment of Angina Pectoris, *Practitioner* **30** 179, 1883.

26 Tainter, M. L., Stockton, A. B., and Cutting, W. C. Use of Dinitrophenol in Obesity and Related Conditions, *J A M A* **101** 1472 (Nov. 4) 1933.

benefit from this regimen. The use of adequate doses of aminophylline or quinidine, however, may obviate the necessity for frequent administration. These two drugs are of value for approximately one half of all patients and for most of those patients who derive benefit from any form of medication. Should these drugs fail to confer sufficient relief or should their use be attended by untoward effects, theophylline calcium salicylate, atropine sulfate or erythrol tetranitrate is worthy of trial before resort is made to surgical procedures (chart 7).

It is evident that the response to medication is no indication as to the prognosis for a given patient. In the present series of twenty-six patients, five experienced attacks of coronary occlusion, and one had congestive failure during the period of observation. Two of these patients died. All but one of these complications occurred at least one month after the patient had stopped all medicinal therapy and could

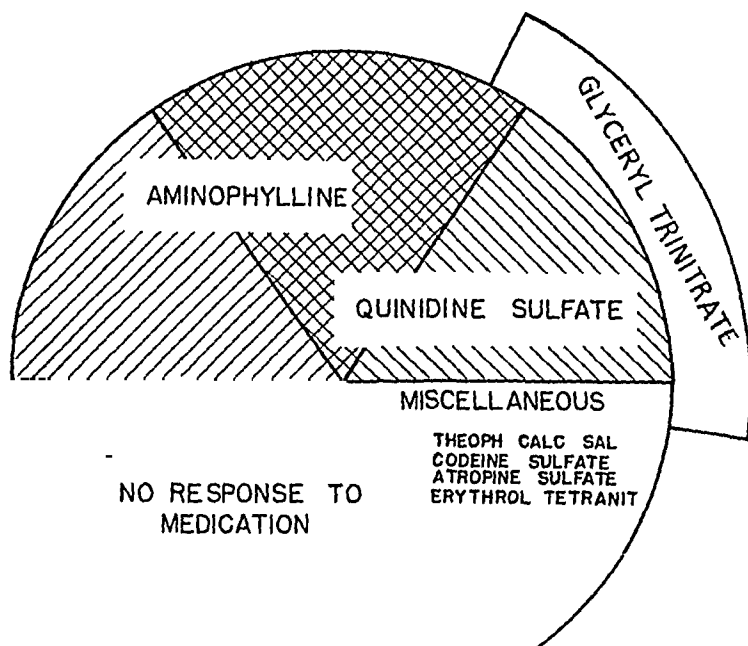


Chart 7—The proportion of patients responding to medication

in no way be attributed to the use of the medication or to the exercise tolerance test. In the remaining patient coronary occlusion developed during the week that he was taking glyceryl trinitrate as a prophylactic against attacks. Three of these patients had shown striking clinical benefit following several different types of medication, the remaining three had shown no response to any of the fifteen drugs.

It is to be remembered that drug therapy is only one factor in the medical management of angina pectoris. In many instances beneficial adjustments can be made in the patient's mode of living, while in other instances the correction of anemia, hyperthyroidism or other physical ailments may be of importance.

SUMMARY AND CONCLUSIONS

The use of fifteen different drugs in the treatment of twenty-six patients with angina pectoris was studied. Each drug was given several times a day for at least a week before its effect was evaluated. The efficacy of treatment was ascertained by the usual clinical methods and also by determining how much work, under standardized conditions, the patient could perform before pain developed. Control observations were made to differentiate between spontaneous remissions and improvement due to treatment.

The patient's estimation of therapeutic benefit indicated that all the drugs were approximately equal in value. Placebos were just as often beneficial as other medicaments.

The exercise tolerance test revealed that patients whose treatment consisted of lactose, sodium bicarbonate, potassium iodide or tissue extract were unable to perform any more work than was possible without medication.

Glyceryl trinitrate given before work was undertaken prevented attacks and enabled many patients to do considerably more work. This prophylactic effect was often of relatively short duration, but attacks were prevented for as long as an hour in many cases. Such patients could be rendered completely free from attacks in daily life by taking glyceryl trinitrate at hourly intervals. For all practical purposes small doses (1/500 grain, or 0.1 mg.) were as valuable as larger doses and were attended by little discomfort.

One half of the patients were benefited by either aminophylline or quinidine sulfate. Aminophylline had to be given in doses of 3 grains (0.2 Gm.) to be effective.

Theophylline calcium salicylate, erythrol tetranitrate and atropine sulfate were often of value, occasionally they benefited patients not helped by either aminophylline or quinidine sulfate. The doses of atropine necessary frequently caused discomfort because of side-reactions.

Codeine sulfate and phenobarbital rarely enabled the patient to do more work before pain developed, but these sedatives appeared to be of aid as an adjunct in the treatment of the patient.

Sodium nitrite and small doses of dinitrophenol were only rarely of benefit. Other more effective drugs are available, and dinitrophenol, even in the small doses used, occasionally gave undesirable side-reactions.

Digitalis was rarely of value and frequently caused a striking increase in anginal attacks.

The following pharmaceutical houses supplied the products used in this investigation: Bilhuber-Knoll Corporation, theophylline calcium salicylate, Burroughs Wellcome & Co., erythrol tetranitrate, and Winthrop Chemical Co., Inc., tissue extract.

NORMOGLYCEMIC GLYCOSURIA DIFFERENTIATED FROM OTHER BENIGN GLYCOSURIAS AND DIABETES MELLITUS

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AND

KENDRICK A SMITH, S M

CHICAGO

This paper presents a review of 3 cases of glycosuria, which we have recently had the opportunity to study, in which the sugar content of the blood was normal. It was our feeling that attention should be called to the necessity of a complete investigation of all cases of glycosuria before the institution of the rigid management required by the diagnosis of diabetes mellitus. The social and financial implications of this disease are well realized even by one not in frequent contact with diabetic patients, and for these reasons alone the diagnosis should be made only after the most careful study and the accuracy of the diagnosis should be suspected if after a sufficient trial careful management is unsuccessful.

Of the nondiabetic glycosurias, that due to a lowered renal threshold for dextrose is the most common, the others, such as pentosuria, lactosuria, fructosuria and galactosuria, will be referred to only briefly.

REVIEW OF THE LITERATURE

Normoglycemic glycosuria is known in the clinical literature as renal diabetes, renal glycosuria, benign glycosuria and orthoglycosuria. Von Noorden¹ has used the term normoglycemic glycosuria and Hjarne² the term orthoglycosuria, and these are perhaps the ones of choice, as they describe this clinical entity without giving any misleading suggestion as to its pathologic nature. As the name implies, the condition is one in which sugar appears in the urine in amounts detectable by the usual qualitative tests while the sugar content of the blood does not rise above normal limits at any time. Though the renal

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1 von Noorden, C, and Isaac, S. *Die Zuckerkrankheit und ihre Behandlung*, ed 8, Berlin, Julius Springer, 1927

2 Hjarne, U. A Study of Orthoglycaemic Glycosuria with Particular Reference to Its Hereditability, *Acta med Scandinav* 67 422, 1927

threshold is lowered for dextrose in this condition, no pathologic observations have yet been described which permit its diagnosis at autopsy.³ The threshold may be lowered to a degree permitting constant glycosuria, called by Malmros⁴ glycosuria innocens and by Holst⁵ renal diabetes, or the glycosuria may occur only after meals, when the sugar content of the blood is elevated above the fasting level. To this these same authors have given the name cyclic glycosuria and cyclic renal glycosuria.

The literature indicates this condition to be rather rare. Fowler,⁶ in his summary of cases at the Montreal General Hospital, stated that the incidence is 1.75 per thousand cases of glycosuria, and he quoted the incidence of the revised figures from Joslin's clinic as being 1.66 per thousand cases of glycosuria. There appears to be no particular age group in which a majority of these cases occur. In those reviewed by Marble⁷ from Joslin's clinic the average age at the time of onset was 19.9 years. The youngest patient was reported on by Paullin and Bowcock, quoted by Fowler.⁶ In this case glycosuria was discovered when the patient was 2 years of age and had been constantly present for twenty years since then. Younger patients in whom glycosuria has been discovered have been reported on, but the glycosuria was only transient. For a more complete bibliography of this subject the reader is referred to Marble's excellent paper on "Renal Glycosuria."

DIAGNOSTIC CRITERIA

The criteria for the diagnosis of normoglycemic glycosuria have been given by many authors and may be summarized as follows:

1. The reducing substance in the urine must be identified as dextrose. Pentosuria, lactosuria, fructosuria and galactosuria may occur, but unless dextrose is found in abnormal amounts without hyperglycemia, renal glycosuria is not present.

2. Glycosuria must occur without hyperglycemia and may be constant or may occur only during the postprandial period as a cyclic glycosuria.

3. Fitz, R. Renal Diabetes, in Christian, H. A., and Mackenzie, J. Oxford Medicine, New York, Oxford University Press, 1931, vol. 4, pt. 1, p. 178 (13).

4. Malmros, H. A Study of Glycosuria with Reference to the Interpretation of the Incidental Finding of a Positive Reduction Test, *Acta med. Scandinav. supp.* 27, 1928, p. 1.

5. Holst, J. E. Investigations into Benign Glycosuria and Diabetes Mellitus, *Acta med. Scandinav.* 63: 47, 1925.

6. Fowler, A. F. Renal Diabetes, *Ann. Int. Med.* 7: 518, 1933.

7. Marble, A. Renal Glycosuria, *Am. J. M. Sc.* 183: 811, 1932.

3 The level of the sugar in the blood during fasting and the results of a standard dextrose tolerance test must be normal. This of course takes into consideration the effect of emotion or illness, which may greatly increase the blood sugar.

4 Symptoms suggestive of diabetes mellitus must be absent or explainable by some process such as hyperthyroidism, which may cause loss of weight, weakness and hunger.

5 There should be, ideally, no family history of diabetes mellitus. The history of glycosuria in the family, however, often aids in making the correct diagnosis, as the familial characteristic is common in renal glycosuria.⁵

6 There should be little or no relation between the intake and the excretion of sugar. This holds true for the case in which there is marked and constant glycosuria, but when the glycosuria is cyclic the excretion of sugar will follow to some extent the intake of sugar and the rate of absorption.

7 The rate of utilization of sugar should be normal. However, as has been pointed out by Rabinowitch⁸ and Paullin,⁹ persons with mild diabetes often show no changes in the respiratory quotient which would aid in differentiating them from nondiabetic persons.

8 The patient must not subsequently show diabetes. Rabinowitch⁸ gave no time limit, but Joslin has fixed it at a maximum of three years from the time the diagnosis of renal glycosuria is made. It of course cannot be made too long, for every person has a chance of about 1 per cent that the disease will develop.

MATERIAL AND METHODS OF STUDY

Three patients were investigated because of continued glycosuria of varying degree with what seemed adequate diabetic management. One of the patients, who was being treated with insulin, continued to have marked glycosuria and at the same time to complain of insulin-like reactions. Single determinations of the sugar content of the blood during treatment for diabetes mellitus disclosed that symptoms of hypoglycemia occurred at times when there was definite hypoglycemia, and at no time was there found an abnormal sugar content, as might be expected in a case of diabetes mellitus with constant glycosuria. The other patients presented problems of a somewhat different nature. They apparently had mild diabetes, and the condition should have been satisfactorily controlled with diet therapy. Never had there been sufficient glycosuria to warrant the use of insulin for these middle-aged persons, and never had dietary shifts in the carbohydrate-fat ratio or in the total food content been sufficient to change markedly the degree of glycosuria.

8 Rabinowitch, I. M. The Diagnosis of Renal Glycosuria, *Canad. M. A. J.* 22: 329, 1930.

9 Paullin, J. E. Glucose Utilization in Renal Glycosuria, *Arch. Int. Med.* 37: 88 (Jan.) 1926.

The methods of study used in making the differential diagnosis were those at hand in the nutrition laboratory,¹⁰ namely, the determination of the dextrose content of capillary blood at frequent intervals, usually every fifteen minutes, for a period of from three to four hours after a dextrose test meal, the collection of urine at times corresponding to the capillary punctures and the identification and determination of the amounts of reducing substances present

Analyses were made for capillary blood by the micromethod of Folin and Svedberg,¹¹ which is accurate for values ranging from 40 to 350 mg per hundred cubic centimeters. One modification was added to this method by collecting and oxalating the blood in small funnels before samples were taken for analysis

The urine was analyzed qualitatively by Benedict's alkaline copper solution and quantitatively by the method of Shaffer and Hartmann¹² when the qualitative tests of the specimens were positive for dextrose. Fermentation tests were used to identify the reducing substances. Each twenty-four hour specimen which the patient brought to the laboratory on the day of an examination was analyzed quantitatively

The intake of food of each subject was weighed or measured for a long period prior to the study. The carbohydrate content was calculated, and known additions were made according to the method suggested by Woodyatt¹³ for the diagnosis of latent or mild diabetes mellitus

The dextrose test meal in each case consisted of 1 Gm of dextrose per kilogram of standard body weight and was given in a solution made up to 400 cc and flavored with lemon juice

REPORT OF CASES

CASE 1—In a 34 year old married woman glycosuria was found in 1922 during her stay in a hospital because of spontaneous abortion. After this discovery she was placed on a qualitatively restricted diet until the summer of 1933. Throughout this period there was a strong reduction of the urine at each analysis made by her physician, regardless of how severely the intake of carbohydrate had been restricted. During this period she noticed growing weakness, loss of weight and frequent boils. There was no polyuria or polyphagia. In the summer of 1933 she was given a diet of 70 Gm of carbohydrate and 9 units of insulin twice daily, but even under this management the urine continued to show three and four plus reduction whenever tested. On her first visit to this clinic she complained of weakness and nervousness

On physical examination at the time of her admission to the clinic, on Dec 4, 1933, she was found to be a tired and nervous woman, measuring 165 cm in height and weighing 56.1 Kg. The blood pressure was 110 systolic and 68

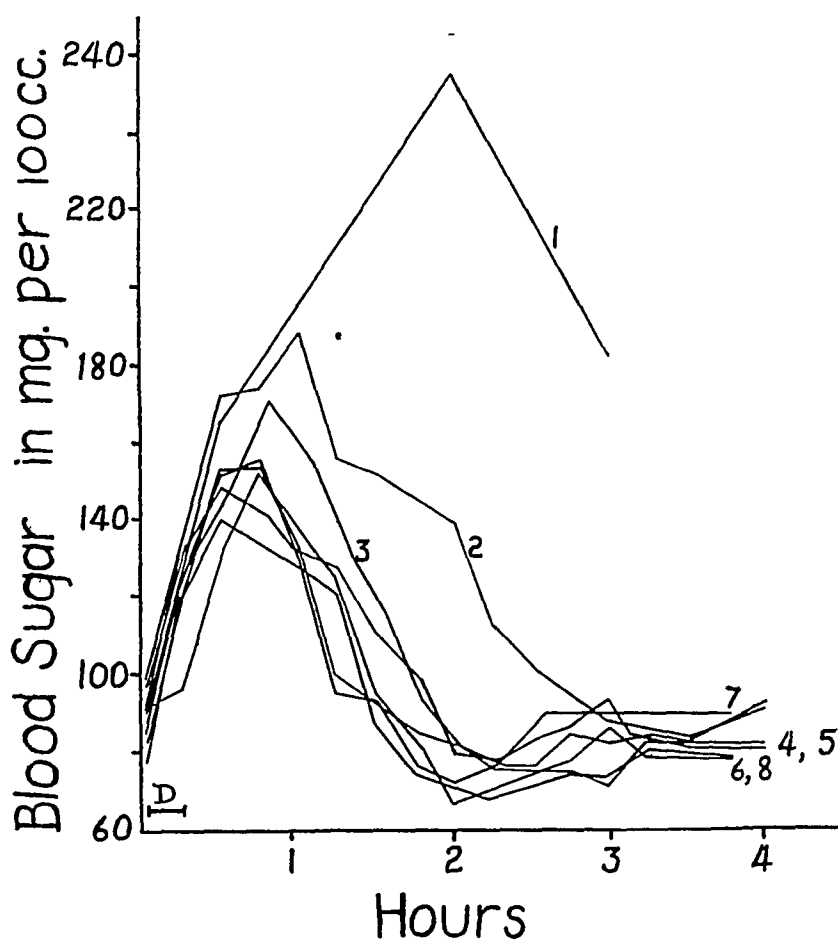
10 Laboratory of F. H. Smith in the Department of Medicine, the University of Chicago

11 Folin, O., and Svedberg, A. Micro Methods for the Determination of Non-Protein Nitrogen, Urea, Uric Acid, and Sugar in Unclaked Blood, *J Biol Chem* **88** 85, 1930

12 Shaffer, P. A., and Hartmann, A. F. Methods for the Determination of Reducing Sugars in Blood, Urine, Milk and Other Solutions, *J Biol Chem* **45** 365, 1921

13 Woodyatt, R. T. Some Milder Forms of Diabetes with Special Reference to Mild Diabetes in Elderly Persons with Arteriosclerosis, *South M J* **17** 145, 1924

diastolic The thyroid gland was palpable, and a basal metabolism test made later showed a rate of +15 per cent Laboratory examination showed 4,080,000 red blood cells, 79 per cent hemoglobin and 6,500 white blood cells The Wasser-



Glycosuria								Curve	
+	++			+++		+++		1	
±	++	++	++	+++	++		+	±	2
±	++	++	++	+	+	±	±	±	3
+	+++	+++	+++	++	+	++	++	++	4
++	+++	+++		+++	+++	+++	+++	++	5
+++	+++	+++	+++	+++	+++	+++	+++		6
++	++	+++	+++	+++	+++	+++	+++	+++	7
+		++	+++	+++			+	+	8

Fig 1 (case 1)—Dextrose tolerance tests D represents a dextrose meal of 50 Gm

mann and Kahn tests were negative Analysis of a single specimen of urine revealed a trace of sugar, while the twenty-four hour specimen which the patient brought in contained 7 Gm of sugar and a trace of acetone The sugar content of the blood during fasting was 92 mg per hundred cubic centimeters

On her second visit to the clinic the dextrose test meal was given, because the symptoms at the time suggested some atypical glycosuria. The results are shown in figure 1, curve 1. It was a typically diabetic curve, and a diagnosis of diabetes mellitus was made on its basis, insulin and diet therapy were continued as before. Table 1 is a brief of the metabolic study made in the outpatient department.

Ten months after this first dextrose tolerance test, studies of the blood sugar relative to the effect of exercise in diabetes mellitus were made for the patient. The results of these experiments are seen in figure 2. Examination of these curves for blood sugar showed that, with the exception of higher levels during

TABLE 1—Data for First Patient Obtained in Outpatient Department

Date	Weight, kg	Urine, 24 Hr, Gm	Car- bohy- drate, Gm	Pro- tein, Gm	Fat, Gm	Cal- ories	Dex- trose, Gm	Insulin			Comment
								A	M	P	
12/ 4/33	56.1	7.0	90	68	157	2,045	145	15	0	15	Trace of acetone, fasting blood sugar, 92 mg per 100 cc
12/11/33	55.0	20.9	80	62	146	1,882	131	15	5	10	Dextrose test meal, curve 1, fig. 1
12/21/33	53.9	6.7	90	68	157	2,045	145	10	5	10	Basal metabolic rate, +15%
12/29/33			90	68	157	2,045	145	10	5	10	Basal metabolic rate, +17%, compound solution of iodine, 5 drops, 3 times a day
1/12/34	54.1	Trace	90	68	157	2,045	145	10	5	10	Complaints of weakness
2/12/34	55.4	Trace	90	68	157	2,045	145	10	10	10	Complaints of weakness
3/26/34	54.5	15.0	90	68	186	2,306	148	10	10	10	Complaints of weakness
4/23/34	54.0	7.6	90	68	186	2,306	148	10	10	10	Complaints of weakness
5/21/34	53.6	Trace	90	68	186	2,306	148	10	10	10	Complaints of weakness
6/15/34			45				45	25	30	16	Hospitalized for dilation and curet tage, mild ketosis
7/ 9/34	50.8	1+						10	10	10	

fasting, the curves were within normal limits. The finding of a constant and rather marked glycosuria at these normal levels for blood sugar led to a diagnosis of renal or normoglycemic glycosuria. At the time this study was made the patient was on a diet of 100 Gm of carbohydrate, 72 Gm of protein and 213 Gm of fat. She was taking 10 units of insulin before breakfast, 10 units at noon and 10 units before the evening meal.

The day on which the last curve for blood sugar with exercise was made the patient entered the hospital so that a more complete analysis could be carried out and the possibility of well controlled diabetes mellitus accompanying the normoglycemic glycosuria could be investigated. The results of these tests are shown in figure 1. Table 2 gives a summary of the dietary changes and the amount of sugar found in the urine during the patient's stay in the hospital.

A diagnosis of uncomplicated normoglycemic glycosuria was made on Nov 15, 1934, and the patient was asked to test the urine of her blood relatives. Her

mother and two sisters were found on several occasions to have postprandial glycosuria of one plus reduction. Further investigation would have been interesting but could not be carried out.

TABLE 2—Data for First Patient During Hospitalization

Date	Weight, Kg	Urine, 24 Hr		Diet						Blood Sugar, Mg per 100 Cc			Comment
		Gm	Total Nitro- gen, Gm	Creati- nine, Gm	Car- bohy- drate, Gm	Pro- tein, Gm	Fat, Gm	Cal- ories	Dex- trose, Gm				
										8 A M	10 A M	Noon	
11/ 6/34		4.7	9.36	1.13	100	72	213	2,605	162				Blood sugar curve 4, fig 2, insulin, 0, 10, 0 units
11/ 7/34		11.1	10.50	1.22	100	72	213	2,605	162				No insulin
11/ 8/34		13.9	10.80	1.24	100	72	213	2,605	162	84	101	91	
11/ 9/34		13.1	11.73	1.17	100	72	213	2,605	162	102	95	90	
11/10/34		20.6	11.59	1.23	200	72	213	3,005	262				Dextrose test meal, fig 1, curve 2
11/11/34		16.0	11.53	1.18	200	72	213	3,005	262				
11/12/34		17.5	11.26	1.18	200	72	213	3,005	262	94	93	88	
11/13/34	50.2	27.4	11.00	1.28	250	72	213	3,205	312	90	112	91	Basal meta- bolic rate, +12%
11/14/34		23.0	11.10	1.23	300	72	213	3,405	362	98	91	97	
11/15/34		21.0	11.55	1.30	300	72	213	3,405	362	100	95	95	Blood sugar at 9 a m , 104 mg , fig 1, curve 3

TABLE 3—Data for First Patient Obtained Subsequently in Outpatient Department While on General Diet

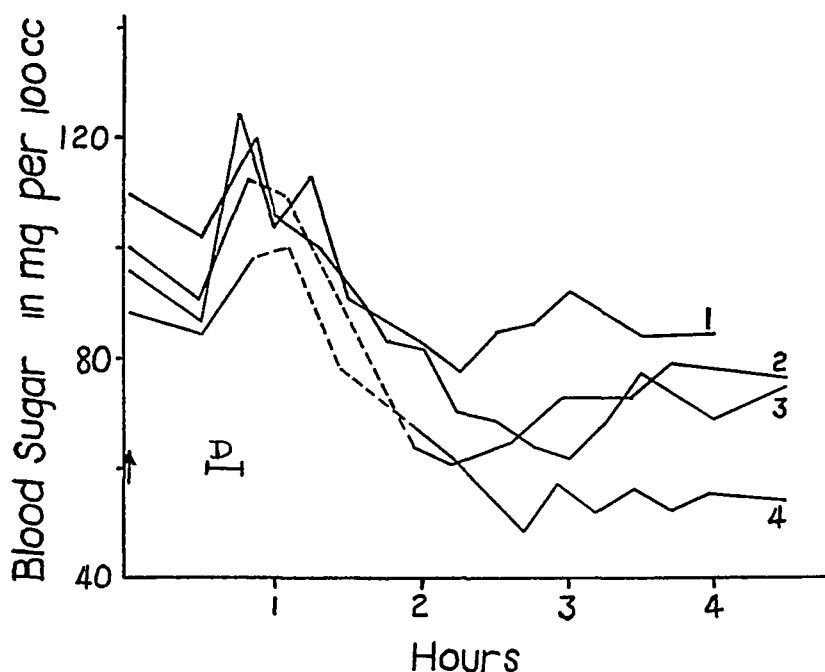
Date	Weight, Kg	Urine, 24 Hr			Comment
		Dextrose, Gm	Total Nitrogen, Gm	Creati- nine, Gm	
1/ 6/35		36.2	9.50	1.10	No ketosis
1/ 7/35		49.4	11.08	1.33	No ketosis
1/11/35		30.5	8.80	1.76	No ketosis
1/12/35		5.9 (4 hr)			Dextrose test meal, fig 1, curve 4
2/17/35		19.3	9.64	1.68	4 month pregnancy, curve 5, fig 1
2/18/35	53.6	22.4	8.12	1.76	No ketosis
4/14/35	58.4	51.0	11.14	1.09	No ketosis
4/15/35		55.0	11.42	0.90	No ketosis, dextrose test meal, fig 1, curve 6
4/16/35					
5/24/35		51.2	9.27		No ketosis
6/19/35		44.6	8.89	0.79	No ketosis
6/20/35		52.0	8.53	1.08	No ketosis
6/21/35					Dextrose test meal, fig 1, curve 7

Since her discharge from the hospital, on Nov 15, 1934, the patient has been on a general diet, and table 3 is a brief of her frequent visits to the outpatient clinic.

It is interesting to note the increased glycosuria as the pregnancy, which was first diagnosed on Feb 17, 1935, progressed. Several studies of the blood sugar and urine of the infant were made when she was 1 month old, both before and after feeding, but no abnormal values or glycosuria were found.

REPORT OF CASES

Snoeck¹⁴ in a series of 2,200 cases of pregnancy found an incidence of 3 per cent for glycosuria and of 1 per cent for lactosuria. Ninety-



Glycosuria								Curve	
-	##	+	±	±	±	±	±	1	
+	+	±	±	-	±	±	±	2	
+	##	##	+	±	±	±	±	±	3
+		+		±	±	±	±	±	4

Fig 2—In figures 2 to 4 the solid line represents a period of rest and the dash line a period of work. For curve 2 there was 3,010 Kg meters of work, and in curve 4 there was 3,275 Kg meters. D represents a mixed meal of 32 Gm of carbohydrate, 14 Gm of protein and 56 Gm of fat. The arrow indicates the administration of 10 units of insulin.

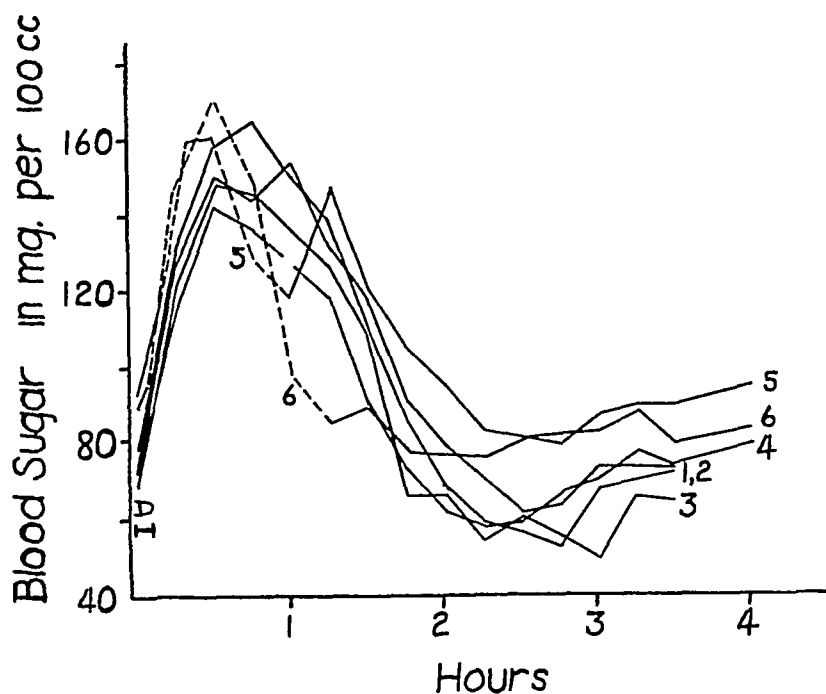
five per cent of the instances of glycosuria occurred in the latter half of pregnancy. Williams¹⁵ in an earlier study found an incidence of

14 Snoeck, J. J. Recherches sur la glycosurie et la lactosurie gravidiques, Arch internat de med exper 7 349, 1932.

15 Williams, J. T. Some Observations upon the Glycosuria of Pregnancy, Boston M & S J 192 163, 1925.

13.6 per cent in the 500 pregnant women tested. The discrepancy probably occurred because Williams used the Fehling solution, which is more sensitive to the nonreducing substances than is the Benedict solution, which was used by Snoeck.

CASE 2—A 34 year old Jew had been observed in the clinic since October 1929. Glycosuria was discovered accidentally in 1921, and his diet was qualitatively restricted at this time, but glycosuria continued intermittently. In 1924 he had a



Glycosuria								Curve
-	±	+	±	-	-	-	-	1
-	+	++	+	-	-	-	-	2
-	+	+++	++	-	-	-	-	3
-	+	++	-	-	-	-	-	4
-	±	+	+	-	-	-	-	5
-	±	+	+	-	-	-	-	6

Fig. 3—Curve 5 represents 9,126 Kg. meters of work, and curve 6 represents 14,220 Kg. meters. D represents a dextrose meal of 66 Gm.

cholecystectomy and an appendectomy, and during his subsequent stay in the hospital traces of sugar were occasionally found in the urine. The values for blood sugar during fasting ranged from 77 to 90 mg. per hundred cubic centimeters. His diet was more rigidly restricted, but occasionally glycosuria was noted.

During 1929 he experienced epigastric distress, and after he was started on a modified Sippy diet, a dextrose tolerance test was given, with entirely normal results. He had experienced symptoms of hypoglycemia at the third hour. On a

second test during this same year hunger and dizziness were noted at the end of three hours. Forty-five minutes after the ingestion of dextrose for the third test the blood sugar content was 225 mg per hundred cubic centimeters, but symptoms of hypoglycemia were again noted at the third hour.

When first seen at this clinic in 1929 he reported having occasional glycosuria, although he remained on a restricted diet.

On Oct 1, 1929, the patient was found to measure 166.5 cm in height and to weigh 63.1 Kg. There were no outstanding physical findings warranting mention. Laboratory analysis of the blood showed 5,360,000 red blood cells, 12,900 white blood cells, negative Wassermann and Kahn reactions and a fasting level for blood sugar of 88 mg per hundred cubic centimeters. Urinalysis revealed no abnormality. Roentgen examination demonstrated either an ulcer in the base of the bulb involving the pylorus or extensive adhesions involving the entire pylorus and duodenum.

Until June 1931, when one twenty-four hour specimen of urine contained 12 Gm of dextrose, the urine was free from reducing substances. In December 1934 the patient was placed on a general diet with feedings between meals. Urinalysis showed no sugar, and the fasting level for blood sugar was 68 mg per hundred cubic centimeters.

In January 1935 further study was started in the nutrition laboratory, the results of which are shown in figure 3. The first five dextrose tolerance tests were made while the daily intake of food consisted of 170 Gm of carbohydrate, 70 Gm of protein and 120 Gm of fat. The sixth test was made after a period of thirteen days during which there was a daily intake of 220 Gm of carbohydrate, the protein and fat content remaining the same as for the other tests. This increase was made in order to expose mild diabetes mellitus by increasing the postprandial level of the blood sugar and glycosuria as compared with the blood sugar content and glycosuria on the lower intake of carbohydrate.

CASE 3—A 47 year old man was first seen on Jan 19, 1932. His paternal grandmother was known to have had glycosuria, but other than that the family history was unimportant.

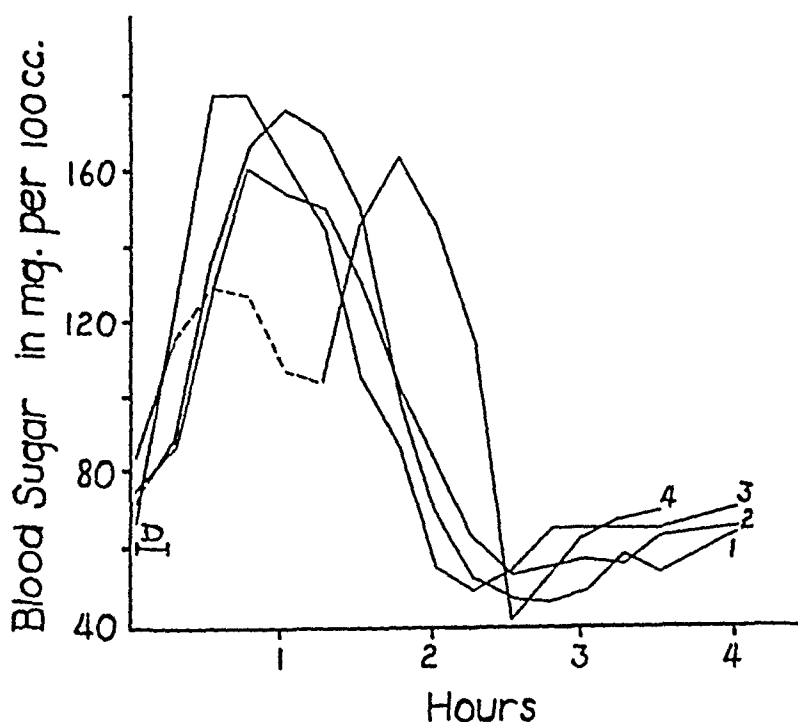
In 1926 the patient weighed 93.5 Kg and was refused life insurance because of hypertension. In 1931 he was found to have symptomless glycosuria and was placed on a qualitatively restricted diet.

On the first visit to the clinic the patient measured 168 cm in height and weighed 77.4 Kg. Studies of the blood showed 5,080,000 red blood cells and negative Wassermann and Kahn tests. The blood pressure was 172 systolic and 130 diastolic. A single specimen of urine was negative for reducing substances. On two succeeding days twenty-four hour specimens of urine were free from sugar, and the fasting level for blood sugar for these two days was 55 and 68 mg, respectively, per hundred cubic centimeters.

There was no exact management for this patient, although he was started on a limited diet of 100 Gm of carbohydrate, 60 Gm of protein and 150 Gm of fat for the first week. Within one month the diet was increased to 250 Gm of carbohydrate, 60 Gm of protein and 150 Gm of fat and maintained for six months. Throughout this time the fasting level for blood sugar was normal, and analysis of twenty-four hour specimens of urine revealed no sugar. Eight months after the initial observation, a dextrose tolerance test was performed and gave normal results, nevertheless, the patient was advised to limit his diet in order to control his weight, which was now 80.1 Kg.

On Jan 9, 1935, the patient was called to the nutrition laboratory for a recheck on the utilization of dextrose. At this time his average intake was approximately

170 Gm of carbohydrate, 60 Gm of protein and 55 Gm of fat. With an intake of about 1,416 calories his weight was 81.3 Kg. A dextrose tolerance test made at this time is recorded in figure 4, curve 1. For six days following this test the patient's diet was increased to a carbohydrate intake of 290 Gm per day by the addition of candy. A second dextrose tolerance test following this regimen is recorded in figure 4, curve 2. The diet was again increased, this time to 410 Gm of carbohydrate, by the addition of candy. This diet was continued for five days, and a third dextrose tolerance test was then made (fig 4, curve 3). The



Glycosuria								Curve
—	—	+	##	±	—	—	—	1
—	—	##	##	+	—	—	—	2
—	—	##	+	—	—	—	—	3
—	—	—	—	—	—	—	—	4

Fig 4—Curve 4 represents 10,850 Kg meters of work. D represents a meal of 70 Gm of dextrose.

diet was then reduced to the usual intake of 170 Gm of carbohydrate per day to prevent a gain in weight, and the fourth test was made while the patient was on this diet.

RESULTS

The diagnosis of normoglycemic glycosuria was established in the first case by the findings for blood sugar and urinary sugar, as shown in figure 2. It is noted that insulin prevented the usual postprandial rise in the level for blood sugar, showing that insulin will lower the level for blood sugar in persons with renal glycosuria as it will in

normal persons Powelson and Wilder¹⁶ have used insulin to lower the level of the blood sugar in cases of normoglycemic glycosuria in which they wished to establish the absolute threshold for dextrose. In our case 1 the threshold was too low to be determined without the use of insulin or exercise to lower the blood sugar content to a point where the urine was free from dextrose.

The metabolism study made in the hospital (table 2) demonstrates the care that was exercised to protect this patient with a history suggestive of diabetes mellitus against further mismanagement. She was hospitalized for study in the nutrition laboratory. Insulin was discontinued cautiously, and determinations of the blood sugar were made at frequent intervals. This process can be followed from the brief of the metabolic study. Normal findings for blood sugar were present throughout this preliminary period. A dextrose test meal was given at this time (fig 1 curve 2). The values for blood sugar were somewhat higher than those for normal persons, but this served only to demonstrate the effect of a lowered intake of carbohydrate preceding the test. The diet was therefore increased by 100 Gm of carbohydrate every three days, a procedure suggested by Woodyatt¹⁸ to aid in the diagnosis of mild diabetes. Dextrose tolerance tests were made while the patient was on diets of 200 and 300 Gm of carbohydrate, and the results are shown in figure 1, curves 3 and 4. These tests demonstrate the normal levels for blood sugar accompanied with constant glycosuria. The patient was discharged with the diagnosis of renal glycosuria and instructed to eat a general diet. She returned at four week intervals bringing two twenty-four hour specimens of urine. Dextrose test meals were given as noted in figure 1. Many of these tests were made while the patient was pregnant but no attempt was made to measure the effect of pregnancy on the renal threshold. The amount of sugar excreted every twenty-four hours particularly during the last trimester of pregnancy, seemed to increase, however, no accurate determination of the intake of carbohydrate was undertaken.

The dextrose tolerance test in case 2 showed slightly higher postprandial peaks than normal. However the findings were not diagnostic of any known metabolic disturbance. Glycosuria was present at some time during each experiment. It did not occur at the fasting level, however. The renal threshold of this subject seemed to be about 140 mg per hundred cubic centimeters. The high value for blood sugar, 225 mg per hundred cubic centimeters (found elsewhere), may have been caused by emotion. During the study of the patient in this laboratory a value for blood sugar of 181 mg per hundred cubic centi-

16 Powelson H C, and Wilder, R M. Innocent Glycosuria, J A M A 96 1562 (May 9) 1931

meters was found during a period of momentary excitement prior to the making of the capillary puncture. This value occurred fifty minutes postprandially, shown in curve 4 (fig. 3). It was not again duplicated. Work did not seem to affect the values for blood sugar in curves 5 and 6, and this also may have been due to emotion, as the patient never became accustomed to riding the stationary bicycle used in these experiments nor could he be reassured regarding the outcome of the tests.

Dextrose was present at some time during each of the tests made for the third patient, except when curve 4 was made, when exercise was performed. As in case 2, this glycosuria was of the cyclic type, that is, it occurred only at the levels for blood sugar found after eating and not at fasting levels. Although the postprandial values for blood sugar were rather higher than those found in many normal persons, the level did not exceed the normal renal threshold for dextrose. Yet there was marked glycosuria at these levels. The threshold for dextrose in this case, as judged from the curves for blood sugar, appeared to be approximately 150 or 160 mg per hundred cubic centimeters.

The histories and experimental work presented in these 3 cases demonstrate that in making the diagnosis renal or normoglycemic glycosuria can easily be mistaken for diabetes mellitus. Case 1 shows this most clearly. Here a history suggestive of diabetes mellitus added to the confusion. However, the benign course of the disease over periods of from nine to fourteen years was not that of diabetes mellitus. The first patient presented symptoms of loss of weight, hunger and weakness, which might be attributed to diabetes, but physical findings were suggestive of intermittent hyperthyroidism, and these were checked by three basal metabolic rates of +15, +17 and +12 per cent.

None of the 3 patients had a family history of diabetes mellitus; the third and particularly the first had excellent family histories for glycosuria. This is to be expected, for the familial characteristics appear more marked in renal glycosuria than in diabetes mellitus. Powelson and Wilder¹⁶ reported that 23 of 91 patients with benign glycosuria showed a family history of glycosuria and said that the incidence would have been higher if the histories had been more complete. Hjarne,¹⁷ in a study of orthoglycemic glycosuria in 199 persons interrelated by blood, described 34 cases of benign glycosuria and 7 cases of diabetes mellitus. Hjarne said he thought that marriage of persons who were probably both subjects of normoglycemic glycosuria produced no "summation" in the direction of diabetes. He concluded that the different forms of glycosuria are inheritable and are transmitted as monofactorial dominant characters but that benign glycosuria and diabetes mellitus have different origins and their occurrence in the same family is a coincidence.

The fasting level for blood sugar in all these cases was normal, with the exception of the fasting level for blood sugar taken when the first patient reported to the nutrition laboratory for the first time. At the time the blood was taken she was almost in a state of collapse and fainted momentarily. Fifteen minutes later the blood sugar was at its usual level. A normal fasting level for blood sugar is a finding on which much of the diagnosis can be based, particularly when a normal fasting level for blood sugar is accompanied with glycosuria, as in case 1. The other 2 patients, while having normal fasting levels for blood sugar, were aglycosuric at these levels.

The lack of correlation between the intake of carbohydrate and the excretion of sugar is well demonstrated by the 3 cases presented. The first patient was the only one to show to any degree an increase in the excretion of sugar with an increase in diet. This did not occur, however, in the same degree as is found in diabetes mellitus.

Respiratory quotients were not determined. The diagnosis seemed assured without these data, and, as has been pointed out by Rabinowitch⁸ and Paullin,⁹ patients with mild diabetes often show no changes in the respiratory quotient which would aid in differentiating them from nondiabetic persons.

SUMMARY

Three cases of normoglycemic glycosuria are reported, and a simple but adequate method of establishing such a diagnosis is presented. This method consists of frequent analyses of the sugar content of the blood by the microcolorimetric method of Folin and Svedberg and simultaneous urinalyses before and after a dextrose meal. The use of the Woodyatt forcing diet preceding the dextrose tolerance tests, as a means of excluding mild diabetes mellitus is demonstrated.

SICKLE CELL ANEMIA IN THE WHITE RACE

IMPROVEMENT IN TWO CASES FOLLOWING SPLENECTOMY

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Sickle cell anemia until recently has been thought to be limited to the Negro race. Even in this race it is relatively uncommon, although about 7 per cent of Negroes show sickling of the red blood cells when a film of fresh blood is sealed under a cover slip for several hours (latent sickling).¹ The trait of sickling is an inborn defect² in the erythrocyte so it is fundamentally a disturbance of the bone marrow, just as the characteristic spherocytosis of congenital hemolytic icterus is an anatomic defect in the formation of erythrocytes.³ If sickle-shaped cells circulate in the blood stream, they are rapidly filtered out of the circulation by the spleen, just as are the spherocytes in congenital hemolytic icterus. The anemia characteristic of meniscocytosis is hemolytic anemia with good response of the marrow, since the bilirubin content of the blood plasma is increased and the bone marrow is overactive, as demonstrated by the hyperplasia noted at autopsy and at biopsy and by the reticulocytosis characteristic of the disease. Anemia does not develop if the sickling trait is latent, as shown by the absence of sickle cells in stained blood films and the development of sickling only in fresh preparations. The spleen early in the disease is uniformly enlarged, but later it is small and at times becomes almost completely atrophic as a result of fibrosis.

There has been no known effective treatment for sickle cell anemia. The patients do not respond to iron or liver therapy. The indication in treatment is to stop the excessive hemolysis, and in this respect the disease again resembles congenital hemolytic jaundice. If the anemia

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1 Graham, G. S., and McCarty, S. H. Sickle Cell (Meniscocytic) Anemia, *South M J* **23** 598-607 (July) 1930

2 Sydenstricker, V. P. Sickle Cell Anemia, *J A M A* **83** 12-17 (July 5) 1924

3 Haden, R. L. The Mechanism of the Increased Fragility of the Erythrocytes in Congenital Hemolytic Jaundice, *Am J M Sc* **188** 441-449 (Oct) 1934

is due to rapid filtering out of the cells by the spleen, splenectomy should be valuable, just as it is in spherocytic jaundice if performed at the proper time, provided some other part of the reticulo-endothelial system does not take over the function of disposing of excessive cells after removal of the spleen. The spherocyte of congenital hemolytic icterus seems to function just as well as an oxygen carrier as the normal biconcave disk, so after splenectomy there is no excessive hemolysis, although spherocytosis persists. By analogy, the sickle cells should function equally well as normal cells and might remain for the normal span of thirty days after the filter was removed. If the cells in sickle cell anemia fragment more readily than normal, the excessive destruction of red blood cells will persist after splenectomy, since fragmented cells are disposed of by other parts of the reticulo-endothelial system after splenectomy.

In the past few years several cases of sickle cell anemia have been reported in white patients in whom there was no suspicion of Negro blood, although this possibility can never be absolutely disproved. Recently also splenectomy has been employed for a small group of patients with sickle cell anemia, without conclusive results as to its value. The two cases recited herewith are reported because they are instances of the disease in the white race and the patients have been markedly benefited by splenectomy.

Only six cases of sickle cell anemia in the white race have been reported, if the doubtful cases of Castana,⁴ Archibald,⁵ Stewart,⁶ Lawrence⁷ and Sights and Simon⁸ are excluded. Cooley and Lee⁹ reported the first case in 1929. Their patient, of Greek parentage, was 4 years of age and showed jaundice and enlargement of the spleen. Rosenfeld and Pincus¹⁰ reported on a patient of Italian origin who was 9 years old. The two patients reported on by Clarke¹¹ were

4 Castana, V. I gigantociti e le anemia semilunari, *Pediatrics* **33** 431-440, 1925

5 Archibald, R. G. Sickle Cell Anemia in the Sudan, *Tr. Roy. Soc. Trop. Med. & Hyg.* **19** 389-391 (Jan.) 1926

6 Stewart, W. B. Sickle Cell Anemia. Report of Case with Splenectomy, *Am. J. Dis. Child* **34** 72-80 (July) 1927

7 Lawrence, J. S. Elliptical and Sickle-Shaped Erythrocytes in Circulating Blood of White Persons, *J. Clin. Investigation* **5** 31-49 (Dec.) 1927

8 Sights, W. P., and Simon, S. D. Marked Erythrocytic Sickling in White Adult, Associated with Anemia, Syphilis and Malaria. Report of Case, *J. Med.* **12** 177-178 (June) 1931

9 Cooley, T. B., and Lee, P. Sickle Cell Anemia in a Greek Family, *Am. J. Dis. Child* **38** 103-106 (July) 1929

10 Rosenfeld, S., and Pincus, J. B. Occurrence of Sicklemia in White Race, *Am. J. M. Sc.* **184** 674-682 (Nov.) 1932

11 Clarke, F. Sickle Cell Anemia in White Race with Report of Two Cases, *Nebraska M. J.* **18** 376-379 (Oct.) 1933

brothers, aged 11 and 3 born of Sicilian parents Cooke and Mack¹² reported on siblings, aged 1 year and 3½ years of white American-born parents In each instance a careful investigation was made to exclude Negro ancestry though this cannot be absolute

Splenectomy as a therapeutic measure in sickle cell anemia has been performed in few instances since first suggested by Sydenstricker¹³ The literature on splenectomy has been well reviewed by Ching and Diggs,¹⁴ who reported an attempted splenectomy in an 18 year old Negress In this instance the spleen was so small it could not be found, and the patient died soon after the exploratory operation Only ten cases have been reported in which splenectomy has been performed¹⁵ All the splenectomies have been performed on young children and in most instances the spleen has not been excessively large The weights recorded have been 186 and 194,^{15c} 621^{15e} 655¹⁵ⁱ 112,¹² 200^{15f} and 295 Gm,^{15g} respectively In Stewart's case⁶ the spleen had been large but was small at the time of operation In Hahn's cases,^{15b,d} the size of the spleen was recorded as three and four times, respectively, the normal adult size It is interesting to note that the greatest improvement has followed the removal of large spleens In none of the cases, when reported, had the patient originally been followed long enough to determine the ultimate value of splenectomy Landon and Patterson,¹⁵ⁱ in reporting a case recently, summarized the end-results in cases

12 Cooke, J V, and Mack, J K Sickle-Cell Anemia in White American Family, *J Pediat* **5** 601-607 (Nov) 1934

13 Sydenstricker, V P Sickle Cell Anemia, *South M J* **17** 177-183 (March) 1924

14 Ching, R E, and Diggs, L W Splenectomy in Sickle-Cell Anemia Report of Case with Necropsy in Adult on Whom Splenectomy Was Attempted, *Arch Int Med* **51** 100-111 (Jan) 1933

15 (a) Hahn, E V, and Gillespie, E B Sickle Cell Anemia Report of Case Greatly Improved by Splenectomy Experimental Study of Sickle Cell Formation, *Arch Int Med* **39** 233-254 (Feb) 1927 (b) Stewart⁶ (c) Bell, A J, and others Sickle Cell Anemia Reports of Two Cases in Young Children in Which Splenectomy Was Performed, *Am J Dis Child* **34** 923-933 (Dec) 1927 (d) Hahn, E V Sickle Cell (Drepanocytic) Anemia with Report of Second Case Successfully Treated by Splenectomy and Further Observations on Mechanism of Sickle-Cell Formation, *Am J M Sc* **175** 206-217 (Feb) 1928 (e) Landon, J F, and Laman, A V Sickle-Cell Anemia with Case Report of Splenectomy, *ibid* **178** 223-228 (Aug) 1929 (f) Levy, F E, and Schnabel, T G Abdominal Crises in Sickle-Cell Anemia, *ibid* **183** 381-391 (March) 1932 (g) Bothe, F A Splenectomy for Sickle-Cell Anemia, *Ann Surg* **97** 146-150 (Jan) 1933 (h) Cooke and Mack¹² (i) Landon, J F, and Patterson, H A Evaluation of Splenectomy in Treatment of Sickle-Cell Anemia Late Results of Two Cases So Treated with Summary of Present Condition of All Reported Splenectomized Patients, *J Pediat* **7** 472-477 (Oct) 1935

reported sufficiently long before for a follow-up to be of value. All the patients were living. In Mitchell's case ^{15c} splenectomy, performed six years previously, did "no particular good." In all other cases ¹⁶ the patients were clinically well, although still anemic. Bothe's patient ^{15g} had been splenectomized two years before the report was made and was greatly improved. Our two patients have been followed for fourteen and five years, respectively, since operation. In each instance the splenectomy was performed with an incorrect diagnosis of Banti's disease because of the obscure anemia and splenomegaly. The correct diagnosis was made in a check-up of splenectomized patients when sickle cells were noted in stained blood films and marked sickling was demonstrated in fresh preparations. Further study of the sections of the spleens removed shows many sickle cells in the capillaries.

The parents of the two sisters reported on in this paper were born in Sicily. One patient was born in Sicily, the other in this country. Close questioning elicited no family features suggesting the presence of Negro blood. The parents' families had been associated for generations in Sicily, where there were no Negroes. The father of our two patients died of a blood dyscrasia for which a diagnosis of myeloid leukemia was made, although some unusual features were presented. He had jaundice, an enlarged spleen, marked anemia and leukocytosis, with the development of many myelocytes in the blood after his admission to the hospital. With roentgen therapy the white cell count decreased, but the anemia was progressive, and death occurred when the patient was at home three months after admission to the hospital. The seven children were studied at that time, and our second patient was found to have a large spleen. Unfortunately, the possibility of sickle cell anemia was not considered in the father's case, so no special studies were made. The mother's blood was normal, and the father had a congenital flexion deformity of both little fingers, similar to that in our first patient. Leukocytosis is fairly constant, and myelocytosis is frequent in sickle cell anemia, so it seems possible that the father died of an acute exacerbation of sickle cell anemia with a marked bone marrow reaction. Three other children in the family were examined recently, but no significant physical findings were noted. The blood of one brother showed sickling in fresh preparations, although he had no significant anemia. The history of the flexion deformity of the little finger in the family history is interesting. The occurrence of this anatomic defect in the father of our patients has already been mentioned. A similar deformity was present in the paternal grandfather, a brother, an aunt and two cousins of our patients.

¹⁶ Stewart ⁶ Hahn and Gillespie ^{15a} Bell and others ^{15c} Hahn ^{15d} Landon and Lyman ^{15e}

REPORT OF CASES

CASE 1—A B, now aged 21 years, was first seen when 8 years of age because of loss of appetite, recurrent sore throat, fever, weakness, pallor and jaundice. These symptoms began at the age of 5 years and occurred in attacks lasting one to two weeks. At the original examination she appeared poorly nourished, the scleras were icteric, the spleen extended down to the iliac crest and the tonsils were infected. She then had mild anemia (4,000,000 red blood cells and 70 per cent hemoglobin) and a white cell count of 22,000. The Wassermann reaction was negative. The spleen was removed by Dr G W Crile on Oct 31, 1922. For ten years the patient remained free from symptoms and then was readmitted to the hospital. A diagnosis of rheumatic heart disease with mitral stenosis was made. Physical examination showed mitral stenosis and inefficiency, with a competent heart, and no other significant findings. She has the flexion deformity of the



Fig 1—Photograph of the hands of A B, showing the flexion deformity of the little finger

little finger previously mentioned (fig 1). The findings in the blood are detailed in the accompanying table. Sickie-shaped and oat-shaped cells are always found in stained preparations (fig 2*A*), and fresh preparations on standing show sickling of all cells (fig 2*B*). Blood counts have been made frequently over a period of four years. The number of erythrocytes is usually normal, with a decreased hemoglobin content and color index. There are usually leukocytosis, reticulocytosis and an increase in the bilirubin content of the plasma. A period of intensive intramuscular liver therapy and the administration of 60 grains (3.6 Gm) of pills of ferrous carbonate daily caused no change in the blood picture. She has continued to have pains in the joints that are more characteristic of those in sickle cell anemia than in rheumatic fever, but otherwise she is clinically well.

CASE 2—F B, a sister of A B, was admitted to a hospital at the age of 15 because of increasing splenic enlargement and pallor. She had been told that she had a large spleen when 11 years of age. She had become increasingly weak

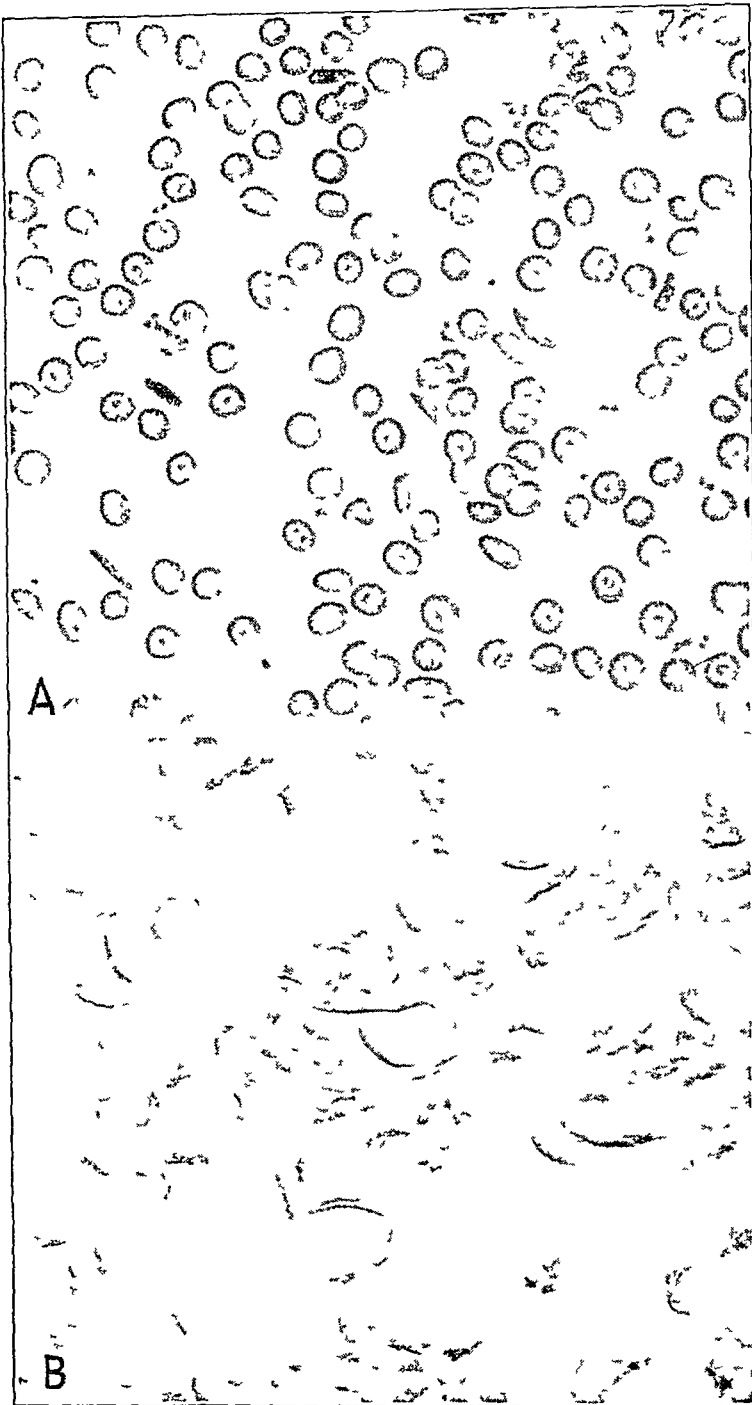


Fig 2—*A*, photomicrograph of a stained blood film in case 1 (*A B*) This picture shows sickle cells and the dimpling of the central area of many red blood cells *B*, photomicrograph of a fresh preparation of blood in case 1, showing sickling of red blood cells

and icteric. On examination there were no significant physical findings, except enlargement of the spleen, which extended down to the iliac crest and nearly to the midline. The edge of the liver was palpable 2 fingerbreadths below the costal margin in the nipple line. The blood count showed 3,690,000 red blood cells, 60 per cent hemoglobin and 6,650 white blood cells. The differential count was not abnormal, and the icterus index was 11. The clinical diagnosis was Banti's disease. The spleen was removed by Dr. Claude S. Beck on July 27, 1931. After the splenectomy there was a stormy course. The anemia became much more marked, and the white cell count rose to 60,000, with myelocytes and many nucleated red blood cells. This postoperative reaction was similar to the blood picture presented by the father without treatment.

The patient has considered herself in good health since the operation, and physical examination now reveals nothing significant. The findings in the blood are given in the accompanying table. The fresh preparations show marked sickling.

Pathologic Study of the Removed Spleen—Case 1. The spleen weighed 480 Gm., had a smooth capsule, was firm and on section cut with considerable resist-

Data on the Blood

Case	Red Blood Cells per Cu. Mm.	Volume of Packed Erythrocytes (% of Normal)	Hemo- globin, Per centage	Color Index	Satura- tion Index	White Blood Cells, per Cu. Mm.	Icterus Index	Reticulo- cytes, Per centage
9/14/ 2	1,900,000	71	0.81	71	0.81	1.00	9,900	8
11/2/ 2	1,580,000	75	0.81	65	0.71	0.87	8,900	10
2/19/ 4	1,670,000	75	0.81	65	0.70	0.87	11,150	20
3/11/ 4	1,600,000	75	0.78	65	0.70	0.89	10,750	15
2/28/ 5	1,850,000	75	0.75	65	0.67	0.89	15,100	15
7/27/ 5	1,470,000	69	0.77	58	0.65	0.84	10,650	15
5/ 8/ 5	1,600,000	75	0.82	61	0.66	0.81	15,550	10
Case 2								
2/18/ 4	1,760,000	77	0.88	65	0.75	0.84	8,600	15
5/11/ 5	4,350,000	75	0.84	61	0.70	0.84	8,800	8
8/11/ 5	1,110,000	69	0.88	58	0.70	0.84	12,750	10

ance, suggesting diffuse fibrosis. On histologic study it showed thickening of the trabeculae and engorgement and hemorrhages in the pulp. Altered blood pigment was seen in numerous wandering cells and polymorphonuclear leukocytes. Material stained bluish black and giving the characteristic reaction for iron with special stains was observed in cells, in masses and in threads associated with trabeculae. In many places most of the material contained in foreign bodies took the stain for iron. The striking feature in the stained reactions was the appearance of chronic diffuse inflammation, with circumscribed areas of degeneration of elastic tissue or trabeculae and deposition of iron pigment.

The diagnosis was chronic diffuse splenitis with considerable deposition of iron pigment.

The sections have been examined again in the light of recent studies of the blood, and many sickle cells have been observed.

Case 2. The spleen weighed 700 Gm. The capsule was smooth but slightly thickened. The spleen showed increased resistance on section. Histologic sections showed the trabeculae slightly increased in thickness, with partial hyalinization. The connective tissue was definitely increased. The cellular pulp tissue was decreased, and a large quantity of blood was present. A section of liver removed at operation showed nothing unusual.

The diagnosis was splenomegaly, with a definite increase in the connective tissue reticulum. A note was made that the histologic appearance was consistent with the clinical diagnosis of Banti's disease.

A recent review of these sections showed marked sickling of the red blood cells in vessels and sinuses.

COMMENT

These two cases seem undoubted instances of the occurrence of sickle cell anemia in the white race. Here, as in the other six cases reported, however, the occurrence of Negro blood cannot be excluded absolutely. It is possible that at some time an admixture occurred, although there is nothing in the history or physical findings to suggest this. The familial occurrence of the flexion deformity of the finger in this family is of great interest, since sickle cell anemia is considered a similar anatomic defect in the shape of the erythrocyte. There seems little doubt that the bone marrow is primarily at fault in this disease and forms red blood cells that are abnormal in shape and perhaps in quality.

It is most difficult to evaluate the efficacy of splenectomy here. Both patients had well marked anemia and symptoms dependent on the anemia prior to operation. Since operation both patients have considered themselves well so far as symptoms referable to the anemia are concerned. The study of the blood of both, however, shows that they have anemia which is not marked enough to produce symptoms. The clinical course of sickle cell anemia is highly variable, it may continue to be mild, or it may run a progressively downhill course. As a rule, patients who are not operated on become steadily worse. There is no way of knowing what course the disease would have taken in our cases if the spleen had not been removed. The patients think they have been much helped by operation, and it is our opinion that they have been. They continue to have excessive hemolysis, however, indicated by the increased icterus index, showing that accelerated filtration of cells by the spleen is not the sole cause of the anemia.

The removal of the spleen, if it is large, is a logical procedure in sickle cell anemia. The disease is a hemolytic disorder, and the spleen early, at least, is one seat of excessive destruction of red blood corpuscles. Hemolysis continues after the spleen becomes small, and the anemia of the disease has not been cured in any patient with splenectomy, although it has become definitely less severe. It is apparent that hemolysis here must be continued by some tissue other than the spleen, probably some other part of the reticulo-endothelial system. The first stage in the normal disposal of red blood cells after the usual span of life in the circulation is fragmentation. The evidence indicates that in sickle cell anemia the red blood cells become fragmented more readily than normal, so there must be two factors in the excessive

hemolysis characteristic of the disease. These are excessive removal of red blood cells from the circulation by the spleen, because of the abnormal shape, and excessive fragmentation in which the spleen has no primary part. It is apparent that there is no indication for removal of the spleen unless it is large. The spleen is probably always large early in the disease. Since there is no other satisfactory treatment of the disease, splenectomy should certainly be tried, if the spleen is large, operation should be undertaken, however, with the realization that it affects only one factor in the excessive hemolysis. There is every indication that removal of a small spleen late in the disease is a great

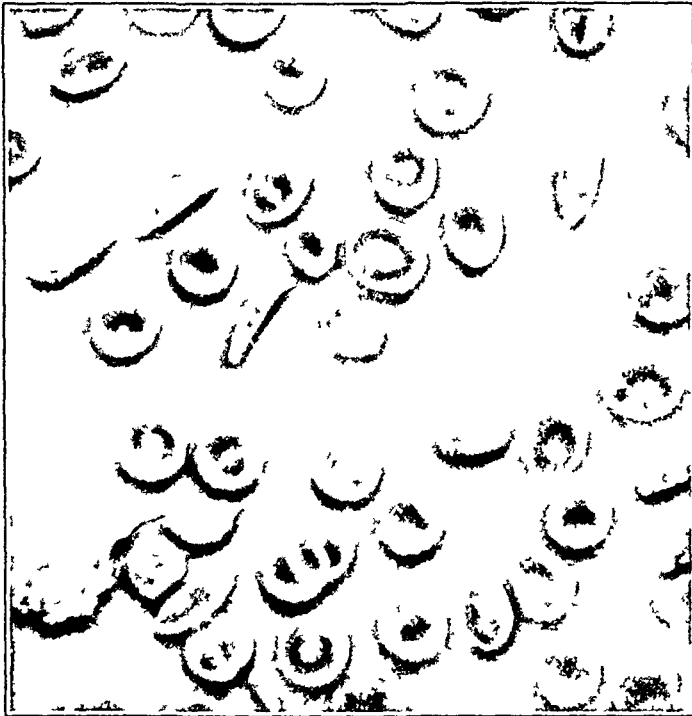


Fig. 3—Bas-relief photomicrograph showing the shape of the dimpled red blood cells in sickle cell anemia

operative risk and is not justifiable. At this stage it cannot have much to do with the excessive destruction of cells.

The two cases reported emphasize again the necessity for considering sickle cell anemia as a clinical possibility in obscure cases of anemia, even in the white race. More cases will certainly be found if searched for.

The slides of the blood of our two patients show clearly a characteristic of the red blood cells in sickle cell anemia which we have not seen referred to in any discussion of the disease. Many of the cells which are not sickled, instead of being biconcave disks, have a central, sugar-loaf elevation, so that a cross-section has the appearance of a Mexican hat instead of the normal dumb-bell. Almost all the illustra-

tions of the blood previously published show this peculiar shape. It is depicted especially well in the illustration of the blood of the patient reported on by Landon and Lyman¹⁷. This effect can be shown best in bas-relief photomicrographs (fig. 3). This unusual shape must be related in some way to the abnormal tendency to hemolysis in sickle cell anemia and may determine the ease of fragmentation. One occasionally sees a few cells of this shape in other anemias, but they are never present in any significant number except in sickle cell anemia. They were constant in all the cases in which we have made an examination.

In our two cases a number of special measurements of the red blood cells were made without finding anything significant. The cell thickness as determined from the mean diameter and volume was normal. The mean diameter was slightly decreased, as was the volume. The volume-thickness index, which indicates the relation of the diameter to the thickness, was normal.

One patient had a thorough trial with liver extract administered intramuscularly and at another time with large doses of iron, neither of which influenced the anemia, so there is evidently no deficiency in specific building material in this disease. The blood of both patients showed beginning hemolysis in a 0.42 per cent solution of sodium chloride, and the hemolysis was not complete in a 0.28 per cent solution, so the fragility was slightly decreased.

SUMMARY AND CONCLUSIONS

Two white patients with sickle cell anemia are reported on.

The patients are sisters, born of Sicilian parents.

There is no history or physical finding suggesting an admixture of Negro blood.

Both patients have had the spleen removed, with marked benefit.

In one case the spleen was removed fourteen years ago and in the other five years ago.

Both patients continue to have mild hemolytic anemia but are clinically well.

In sickle cell anemia there seem to be two factors in the excessive hemolysis characteristic of the disease, viz., excessive filtration of abnormally shaped cells and excessive fragmentation or early death of the cells.

The results obtained in these cases suggest that splenectomy should be employed more often in sickle cell anemia if the spleen is large and the patient is seen early in the disease. It is not a cure but only an aid in treatment since anemia persists.

CLINICAL SYMPTOMS OF CHRONIC GASTRITIS

OBSERVATIONS ON THIRTY-FIVE SELECTED CASES

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Since the demonstration by gastroscopy of the frequent occurrence of chronic gastritis,¹ gastroscopists have often stated that this disease does not show a definite symptom complex - Advanced gastric cancer and chronic round ulcer of the stomach may exist with mild or no subjective complaints, yet it is rare for chronic disease to exist anywhere in the body without being accompanied with some symptoms which aid the physician in his diagnostic attack on the organ involved. In the cases of mildest cystitis some tenesmus or urinary frequency points to possible disease of the bladder, just as diarrhea points to possible disease of the bowel. It would be a rare anomaly if the stomach remained free from all symptoms referable to it in advanced chronic inflammation of its walls.

With the idea of emphasizing a syndrome or at least of indicating symptoms most frequently present in chronic gastritis, we selected for this report from among three hundred and forty-nine patients with chronic gastritis diagnosed by means of the gastroscope at the Billings Hospital, twelve with the superficial and twenty-three with the hypertrophic variety. The atrophic variety was not included because an insufficient number of patients were left after elimination according to our rather rigid requirements. We included no patients who presented a gastroscopic picture of chronic gastritis in whom a demonstrated func-

1 Schindler, R. Die diagnostische Bedeutung der Gastroskopie, München med Wchnschr **69** 535, 1922, Lehrbuch und Atlas der Gastroskopie, Munich, J F Lehmann's Verlag, 1923.

2 Hohlweg, H. Beobachtungen und Betrachtungen auf Grund von 100 Gastroskopen, München med Wchnschr **71** 506, 1924. Gutzeit, K. Die Gastroskopie im Rahmen der klinischen Magendiagnostik, Ergebn d inn Med u Kinderh **35** 1, 1929. Henning, N. Die Entzündung des Magens, Leipzig, Johann Ambrosius Barth, 1934. Moutier, F. Traité de gastroscopie, Paris, Masson & Cie, 1935. Schindler, R., and Ortmyer, M. Classification of Chronic Gastritis with Special Reference to the Gastroscopic Method, Arch Int Med **57** 959 (May) 1936.

tional or organic disorder might account for the symptoms in the digestive tract. This excluded patients with a positive Wassermann reaction, arteriosclerosis, demonstrable gastric or duodenal ulcer, cirrhosis of the liver, cardiac disease, pernicious anemia, marked psychoneurosis, colitis of any variety, disease of the gallbladder, diabetes, carcinoma of the abdominal organs, hypertensive cardiovascular renal disease, migraine and menopausal symptoms and patients in whom combinations of two types of gastritis were found by gastroscopic examination—in short, all patients for whom some other tenable diagnosis could be made, even when we did not always agree that the symptoms should be accounted for on the basis of the other diseases. We wish to emphasize that in the patients eliminated because of the presence of other diseases there was undeniable evidence of chronic gastritis also. Future research will be needed to determine whether the gastric disorder or the other disease was responsible for the abdominal symptoms.

The following tabulation briefly indicates the number of cases and the sex distribution of the two types of chronic gastritis.

Chronic Gastritis

	Males	Females	Total
Hypertrophic variety	22	1	23
Superficial variety	5	7	12
	—	—	—
	27	8	35

Although a few patients were under 30 years of age and a few were over 50, none were younger than 20 or older than 59 years, and twenty-five were in the fourth or fifth decade.

The duration of illness was on the whole prolonged. Only one of the patients (with hypertrophic gastritis) dated the onset of illness a month previously. Twenty-six patients had had symptoms for from two to twenty years, while nine had had symptoms for from one to eighteen months. Patients with hypertrophic gastritis had had an average duration of symptoms of four years. Those with superficial gastritis had had an average duration of symptoms of three and three-fifths years.

Of the twenty-five patients who made definite mention as to periodicity or constancy of the symptoms, four with superficial gastritis had periodic and five had constant (daily) distress. Of those with hypertrophic gastritis thirteen had periodic and three had constant distress.

The symptom most common to all these patients was the location of the distress. Thirty-two of the patients complained of localized distress, twenty-seven referring it to the epigastrium and five to the upper half of the abdomen (two referred it to the right upper quadrant, one to the substernal region and two to the left and right upper quadrants). Two of the remaining three patients stated that their distress

was "general" Radiation occurred rarely (four times) to the lower portion of the abdomen, to the nipples or to the back

The type of distress varied as greatly as it does with ulcer or cancer of the stomach Dull pain, burning, gnawing, vague distress and a feeling of fulness distention or pressure seem to be common symptoms in chronic superficial and hypertrophic gastritis, just as are belching and sour eructations Nausea was mentioned by only four of the patients with hypertrophic gastritis and vomiting by four with hypertrophic and three with superficial gastritis Hematemesis was mentioned by only one patient of the group, he had superficial gastritis, but it is well known that gross gastric hemorrhage may occur in all types of gastritis Severe pain was mentioned by none of the patients with superficial gastritis and by six with hypertrophic gastritis Heartburn, sour regurgitation, "gas" griping, crawling, bloating and borborygmi were occasionally mentioned Loss of appetite and increase of appetite were rare symptoms in this group contrasting with statements of gastroscopists based on larger less rigidly selected material

The distress in relation to the taking of food in patients with superficial gastritis occurred within the first half-hour in five cases and within from one to four hours in six cases Midnight distress was mentioned by one In contrast to the patients with superficial gastritis, none of the patients who had hypertrophic gastritis complained of distress immediately or within thirty minutes following a meal Seventeen complained of the onset from one to four hours after meals Two had midnight distress Two were indefinite, saying their distress occurred "after" meals One mentioned "no relationship" to eating

Aggravation of distress was caused most frequently either by unrestricted or large amounts of food or by certain foods, this factor being mentioned by ten of the thirty-five patients

Relief from distress was obtained by eating far less constantly by these patients than in our experience with patients suffering from chronic uncomplicated benign round gastric or duodenal ulcer Nine (39 per cent) with hypertrophic and four (33.3 per cent) with superficial gastritis, however, had complete and definite relief after eating

Relief from pain by alkali was obtained by eleven (47.8 per cent) of the patients with hypertrophic gastritis and by eight (66.6 per cent) with superficial gastritis, a total of nineteen (54.2 per cent) of the thirty-five patients Vomiting, belching, aspiration and bland diets gave relief in a small proportion of cases

Since all patients with disease that might contribute to the production of abdominal symptoms were eliminated from this review, it is not strange that practically all who were included were free from abnormal physical findings or symptoms referable to other systems Ten men-

tioned "nervousness" of an indefinite sort, a few had headaches and six spoke of a marked loss of weight. They were singularly free from disturbance of bowel function and excessive use of cathartics. Eighteen of the patients had one or two normal bowel movements daily. Six had hard stools and six had mushy or watery stools. The remainder were not specific as to the frequency or nature of the stools. Six of the patients used cathartics oftener than once a week. The only physical finding noted, and that occasionally, was abdominal tenderness (five of the patients with hypertrophic gastritis noted tenderness in the epigastrium, one to the left of the umbilicus, three in the right upper quadrant, four in the left lower quadrant and two in the right lower quadrant, while one of the patients with superficial gastritis noted distress in the upper portion of the abdomen, and one noted it in all four quadrants). It is possible that if mild degrees of tenderness had been carefully searched for they might have been found more often—for instance, the zone of tenderness to the left of and below the umbilicus.³ But it will be noted that many of these patients were examined in departments other than that of gastro-entereology, and in our opinion this gives a better cross-section of signs and symptoms than the more minute investigation of the trained specialist, especially when the histories and results of examinations agree when checked by the cooperating department.

Laboratory procedures for these patients showed negative Wassermann and Kahn reactions and normal urine and blood. Gastric analyses were made for thirty-two of the thirty-five patients. Twenty-two of the patients with hypertrophic gastritis (one not tested) showed free hydrochloric acid by the Ewald or histamine test. Of those with superficial gastritis, nine showed free hydrochloric acid, and one showed no free hydrochloric acid (Ewald test meal), two were not tested. For the thirty-one patients who showed free hydrochloric acid in test meals, the range of free hydrochloric acid was from 11 to 100 points. A negative result for the benzidine test of the stools of thirty patients and a one plus reaction for five patients were recorded.

Roentgenograms of the esophagus, stomach and duodenum of thirty-two of these patients were normal. In one a diagnosis of spastic hour-glass stomach was made, in another, thickening of the gastric rugous folds, and in a third, "marked gastritis" (type not mentioned). In nineteen instances the colon was studied roentgenographically and was normal and in five instances the gallbladder was observed to be normal. It is obvious that lesions of the colon and gallbladder were infrequently suspected, because of the relative infrequency of roentgenographic studies in this series.

3 Schindler, R. Die klinische Diagnose der Gastritis chronica, *Munchen med Wchnschr* 73 482, 1926.

The gastrosopic findings will be reviewed in greater detail, as they represent the positive diagnostic signs for these patients. Of the twelve patients with superficial gastritis, the entire stomach, including the pylorus, was visualized in nine, part of the antrum gastrosopically and the body in two and the region above the angulus in one. In two patients the entire gastric mucous membrane was observed to be involved in gastritic changes; in six there were changes noted above the angulus, and in four there were seen localized or circumscribed areas of gastritis. The degree of gastritis was described as marked in seven and slight in five. Changes in the mucous membrane or in the secretion or both were noted in all patients. Hemorrhage or erosion of the mucous membrane or both were seen in six. Neither the degree of gastritis, i. e. its severity, nor the presence of hemorrhage or erosion was associated with severity or aggravation of distress in these patients.

Of the twenty-three patients with chronic hypertrophic gastritis, the entire stomach with the pylorus was visualized in eighteen, the body and part of the antrum in three and the stomach above the angulus in two. In two patients the entire gastric mucosa was involved in hypertrophic changes; in two only the antrum; in twelve the stomach above the angulus and in the remaining seven some localized or circumscribed area of the stomach. Changes in the mucous membrane typical of hypertrophic gastritis were noted in all of these patients. Abnormal secretion was mentioned for only one. Hemorrhage or erosions of the mucous membrane were seen in seven. Again severity of the gastritis, of the erosions or of the hemorrhage apparently was not associated with an aggravation of symptoms.

In order to illustrate the typical clinical history and picture, we cite in detail the following reports:

CASE 1—D. H., a man aged 35, had symptoms from the time a horse kicked him in the abdomen. The distress, however, did not begin until some time later. For ten years, from spring to winter, while ploughing and engaged in considerable physical exertion, the patient experienced dull midepigastrie pain which came on two hours after meals and lasted for from one to three hours. At times it was so severe in the afternoon that he had to stop work. The pain was relieved by food, milk and fasting. The attending physician regarded this history as "classic for ulcer." Soda, however, aggravated rather than relieved the distress. Ulcer management aggravated it. Pain continued on management of the bowels. An appendectomy four years earlier had not relieved it. The patient was a worrier. He had no other symptoms or past history worthy of note. He had normal stools once daily without catharsis.

Physical examination revealed only epigastric tenderness.

The Ewald test showed free hydrochloric acid of 63 and total acid of 82. The stools were normal. A motor meal showed that there was no retention. The urine and blood were normal. Roentgenograms showed that the esophagus, stomach, duodenum and chest were normal.

Gastroscopic Examination—At first the pylorus was seen, without peristalsis, as a small opening with a reddish edge. The redness was succeeded by gray mucous membrane, which turned to the normal orange. Then vigorous peristalsis began. The antrum was perfectly normal. On the posterior wall the mucous membrane was intensely swollen and contained numerous hemorrhagic stripes and flecks and larger gray and reddish spots. Above this point the mucous membrane of the corpus was normal. In the fornix, especially on the anterior wall, there was seen an extensively thickened and dimpled mucous membrane, with small pits and crevasses.

Diagnosis—The gastroscopic diagnosis was chronic hypertrophic hemorrhagic gastritis of a circumscribed area on the lower posterior wall of the corpus and the anterior wall of the fornix.

The clinical diagnosis, before gastroscopy, was peptic ulcer (?), after gastroscopy it was chronic hypertrophic hemorrhagic gastritis.

CASE 2—W F, aged 32, an electrical engineer, who worked hard and under high tension, seemed to precipitate distress by short periods of excessive use of alcoholic liquors. For six years he had had periodic attacks of severe gnawing to knifelike pain localized to an area the size of the hand in the epigastrium and radiating through to the back at the same level. Usually he had one such period a year, lasting three or four weeks or longer. The pain appeared one or one and a half hours after meals, often three times a day, and was relieved regularly and usually completely by alkali, food and emptying the stomach. Milk taken in the midmorning or afternoon often warded off the distress. Rarely was distress present at night. While under observation but not on treatment, the patient had some severe pain at night.

The remainder of the history showed no relationship to the digestive distress, except for an attack of jaundice of several months' duration when he was 10.

Physical examination revealed only slight tenderness and resistance in the epigastrium.

An Ewald test showed free hydrochloric acid of 70 and total acid of 82. Six benzidine tests of the feces showed a negative reaction, one showed a 3 plus reaction and one showed a 1 plus reaction.

Examinations of the urine and blood revealed no abnormality.

Roentgenographic examination in 1933, after the oral administration of dye, gave faint visualization of the gallbladder. The esophagus, stomach and duodenum were normal. On April 12, 1934, there was normal visualization of the gallbladder (oral dye). The esophagus, stomach and duodenal bulb were normal. On April 18 there was no roentgenographic evidence of a duodenal ulcer.

Gastroscopic Examination—On April 27, 1935, the mucous membrane of the upper part of the stomach was normal, but that of the lower part was markedly swollen and velvet-like.

Diagnosis—The gastroscopic diagnosis was chronic hypertrophic gastritis of the lower part of the stomach. The clinical diagnosis (made after gastroscopy was performed) was suspected gastric or duodenal ulcer. Our diagnosis was chronic hypertrophic gastritis.

CASE 3—E C H, a man aged 33, complained of burning and at times recurring sharp pain in the left upper quadrant of the abdomen for two years, recurring every two to four days and present for the same length of time. He mentioned one interval of five weeks of freedom from pain. His distress came on two or three hours after meals, lasting longer after the noon and night meals than after breakfast, from one-half to two hours, as a rule. A bismuth preparation which he

had been taking for several months, though not until lately during distress, gave him relief from pain in thirty minutes. Two grams of sodium bicarbonate afforded relief from pain within fifteen minutes, as a rule. A full meal usually relieved his distress for two or three hours. The patient thought his distress became worse when he assumed a "fuller" diet. He complained also of occasional dull pains around "the appendix" and of loss of appetite. There was constipation when he was in most distress, and for this he would resort to daily enemas, which neither relieved nor brought on distress. The history otherwise was unimportant.

An Ewald test showed free hydrochloric acid of 27 and total acid of 50. Three benzidine tests of the stools gave negative reactions. Examinations of the blood and urine revealed no abnormality.

Roentgenographic examination showed that the esophagus, stomach, duodenum and colon were normal.

Gastroscopic Examination—The entire stomach, with the exception of the lesser curvature of the antrum, was seen. The antrum was normal. In the greater curvature and in the posterior wall, at the height of the angulus, there were definite changes. The mucous membrane contained large hemorrhages, in which one marked erosion was seen. Grayish spots were noted in the higher parts of the anterior wall.

Diagnosis—The gastroscopic diagnosis was superficial hemorrhagic, erosive gastritis. The clinical diagnosis was the same.

CASE 4—L. M., a woman aged 41, first seen in the clinic on June 17, 1935, was hospitalized on July 5. She complained of periodic distress, localized in the epigastrium, which had been present for years and until the past two weeks had been relieved by taking food and sodium bicarbonate. Previous periods of distress had lasted about two weeks and had recurred at three or four month intervals. The distress for which she came to the clinic was the severest she had had. It came on one or two hours after meals. Food and soda were giving considerable but not complete relief in this attack. The pain was radiating directly through to the back and had awakened her several times at night. At night the pain was relieved by eating. It might occur at 2 a. m., waking her, and recur at 4 and at 6 a. m. No nausea, vomiting or loss of weight was noted. She had a good appetite. Bowel movements were regular without catharsis. There were no other symptoms of significance.

Physical examination revealed only exquisite epigastric tenderness. The temperature and pulse rate were normal.

The Ewald test showed free hydrochloric acid of 47 and total acid of 68. One benzidine test of the feces showed a negative reaction. Three other tests showed a reaction of from 1 to 3 plus. Examinations of the blood and urine revealed no abnormality. The urea clearance test showed a value of 72 per cent. Scratch tests showed a questionably positive reaction for milk products and white of egg.

Roentgenographic examination on June 19 showed that the stomach and duodenum were normal, and on July 8 the stomach, esophagus, duodenum, gall-bladder and colon were shown to be normal.

Gastroscopic Examination—On July 11 the entire stomach, except the lesser curvature of the antrum, was well seen. There was no change in the antrum. The crests of the folds of the lesser curvature, the anterior wall and the body showed marked changes. There were many small red spots and streaks. In the valleys between the folds there were no changes.

Diagnosis—The gastroscopic diagnosis was marked superficial gastritis. The clinical diagnosis was not definitely made. Our diagnosis was chronic superficial gastritis.

The following case report is interesting because of coexistent erosive hypertrophic gastritis and chronic ulcerative colitis. This patient was not included in the group reported on in this paper, because of the complicating ulcerative colitis, hence this report will serve to illustrate the type of case discarded, as well as a combination of gastric and intestinal disorders, the former being entirely forgotten by the attending physician in making the final diagnosis.

CASE 5—E. R., a man aged 32, six months earlier and again for four weeks preceding his first visit to the clinic, experienced epigastric distress coming on regularly from two to four hours after meals, in the midmorning, midafternoon and late evening, and slightly before breakfast. This distress was relieved regularly by food, which he had learned to take even on retiring. A bland diet prevented occurrence of distress. The only significant event in the past history was a short attack of cramps and diarrhea, without the presence of blood being noted in the stools, one year earlier.

Physical examination on Sept. 25, 1934, revealed no abnormality except mild epigastric tenderness.

The Ewald test showed free hydrochloric acid of 43 and total acid of 58—normal values. The benzidine test of the feces showed a negative reaction. The urine and blood were normal.

Roentgenograms showed that the esophagus, stomach and duodenum were normal.

On October 12 the patient returned to the clinic with a new complaint. The epigastric distress had been improved by a bland diet, but mild to severe abdominal cramps had developed on October 10, with three or four loose stools each day. Physical examination added nothing new. Examination of the stools on October 12, 15, 16 and 17 did not reveal *Endamoeba histolytica*.

Gastroscopic Examination—A thick, edematous mucous membrane was seen, with small creases and one small erosion on the anterior wall. Other portions of the stomach were normal.

Further Data—Proctoscopy, on October 26, showed scattered superficial ulcerations with undermined edges, which suggested those of amebic dysentery. After October 26 the stools showed pus and blood (2 plus). No amebas, cysts or ova were found.

On October 31 the patient was hospitalized because of chills and fever and persistence of diarrhea, and a rather stormy course of illness followed. Fever with exacerbations and chill, leukocytosis, diarrhea, anemia requiring transfusions, finally redness of the ankle joints, pain, tenderness and a loss of 22 pounds (10 Kg.) in weight were the chief symptoms. These slowly receded after several months when he was discharged to rest in bed at home. The stools showed no *E. histolytica* or *Bacillus dysenteriae* throughout the patient's stay in the hospital. The feces showed profuse amounts of pus and blood. On November 5 a heavy growth of green streptococci was obtained. Culture of the blood was sterile. There was no agglutination for typhoid or paratyphoid A and B serum. The urine was normal throughout.

In April 1935 the patient's wife wrote that he had gained 40 pounds (18 Kg.)

Diagnosis—The gastroscopic diagnosis, made on Oct 13, 1934, was chronic erosive hypertrophic gastritis. The clinical diagnosis, made on October 31, was chronic ulcerative nonspecific colitis and arthritis, this clinical diagnosis was repeated when the patient was discharged, on Jan 27, 1935.

COMMENT

We selected twelve patients with chronic superficial gastritis and twenty-three with chronic hypertrophic gastritis from among three hundred and forty-nine patients with superficial, hypertrophic and atrophic gastritis, so diagnosed by means of the gastroscope, in order to analyze the clinical pictures in detail. Many more patients might have been included in whom gastritis was found in combination with other disease entities and who referred their symptoms to the gastro-intestinal tract. It is obvious that these symptoms might have been due to the gastritis, but it could be argued that they occurred because of the other diseases present. An insufficient number of patients with "pure" atrophic gastritis—uncomplicated by other disease—were on hand to include an analysis of this form of gastritis.

Observations on patients with a combination of superficial and atrophic gastritis were omitted. This combination has frequently been seen, and in our opinion the atrophic variety is a sequela of the superficial variety.

By analyzing even a few cases of two of the forms of chronic gastritis in their purest and most uncomplicated state, we believe that we are presenting a clinical picture valuable in the differential diagnosis of gastric disease. However, we wish to emphasize that this picture is necessarily incomplete.

Among patients with superficial gastritis, about 50 per cent show periodic distress and 30 per cent constant distress. The distress is located in the upper portion of the abdomen, chiefly epigastric, and is characterized by burning, gnawing, dull pressure or pain. About a third of the patients report distress coming on within the first half hour after eating, while a third have distress from one to three hours after eating. Two-thirds obtain relief with alkali treatment and one-third with food.

About half the patients with hypertrophic gastritis show periodicity of distress. As in those with the superficial variety, the distress is localized in the upper portion of the abdomen, in the epigastrium chiefly. The distress is likely to be severe pain, perhaps in 25 per cent of the patients. The rest report dull, burning or gnawing pain or pressure, not often coming on soon after eating but usually beginning from one to three hours later. About 50 per cent of the patients obtain relief by taking food or alkali.

We fully realize that similar symptoms occur in patients without chronic gastritis or any other demonstrable disease of the stomach or other organs. Among one hundred patients who were gastroscopically normal and who had no demonstrable disease of any other kind, four presented complaints of which the following history and findings are typical.

J. W. H., a man aged 25 years, reported that epigastric burning developed three years previously, usually being present in the morning when he arose, when hot water aggravated the distress. It was relieved, however, almost at once by a full breakfast. Burning recurred from two to four hours after eating and was always relieved by a full meal. Marked belching, occasional bloating and borborygmi were noted but were not distressing. Stools were passed twice daily and were soft and formed. No catharsis or enemas were used. There had been short periods of headache and constipation three years earlier, but these were no longer present. No other symptoms or illness of note was recorded. Physical examination revealed no abnormality, except slight diffuse abdominal tenderness.

The blood, urine and stools were normal. The Ewald test showed free hydrochloric acid of 8 and total acid of 28. Roentgenographically the esophagus, stomach, duodenum and colon were normal.

Gastroscopic Examination—The whole stomach was seen and appeared entirely normal.

Diagnosis—The clinical diagnosis was chronic functional colitis. On reviewing this case we are of the opinion that this clinical diagnosis was not justified.

The predominance of men with hypertrophic gastritis is noted in this small group as well as in earlier reports (Schindler, Henning and others). Though not explained this predominance may afford a clue in the future as to etiology.

The degree of gastritis or extent of gastric involvement bore no regular relationship to the type, severity or frequency of distress in these patients.

Antral gastritis, namely, gastritis confined to the antrum, was noted in only two of the patients included in this report, both of them with the hypertrophic type of gastritis. The marked discrepancy in frequency of antral gastritis between gastroscopic findings on the one hand and surgical material (resection) on the other is again noted though not explained.

In conclusion, we feel justified in stating that until more general use of the gastroscopic method is adopted and numbers of experienced gastroscopists are available, until there is more definite recognition of symptoms actually due to chronic gastritis in its various forms, until more active treatment designed not only to cure symptoms but to ameliorate or cure pathologic conditions of the gastric mucous membrane is persisted in, until the results of treatment are checked as a routine by follow-up gastroscopy and until etiology becomes clearer,

chronic gastritis will remain an unclear clinical entity that will lure medical men on to further exploration. In spite of these limitations, however, chronic gastritis has regained a rightful place in the differential diagnosis of gastric pathologic conditions as a result of the development of a safe endoscopic method of examining the stomach.

SUMMARY

The histories of twelve patients with chronic superficial gastritis and twenty-three with chronic hypertrophic gastritis, selected from a group of three hundred and forty-nine patients, are presented in detail as to subjective symptoms and objective findings including physical, laboratory, roentgenographic and gastrosopic study.

The patients selected for analysis presented no other demonstrable pathologic condition to account for the symptoms.

Four typical case reports are cited of patients with the two types of gastritis, as well as that of a patient with a typical history but with some other disease complicating the gastritis and one of a "normal" patient with similar complaints but without demonstrable disease.

Comment is made on the similarity and differences of histories in the chronic superficial and in the hypertrophic form, on the predominance of men with hypertrophic gastritis, on the lack of correspondence between the extent and severity of gastritis and the severity of symptoms and on the observation of only two patients in this group with gastritis limited to the antrum.

EFFECT ON THE ELECTRO-ENCEPHALOGRAM OF CERTAIN DRUGS WHICH INFLUENCE NERVOUS ACTIVITY

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The electro-encephalogram is analogous to the electrocardiogram, it is a record of the electrical potentials originating in the brain. Hans Berger¹ demonstrated the feasibility of "leading off" these potentials through the intact human skull and made records of them in various neurologic and pharmacologic conditions.

In work already published we² (together with Hallowell Davis) have reported the changes of electrical potential which accompany impaired consciousness, either when occurring spontaneously, as in petit mal, or when induced by means of syncope, anoxemia or hyperpnea. We now wish to report the changes resulting from the administration of various drugs. Our observations follow those of Berger^{1c h} as regards certain of the drugs and those of Loomis and Harvey³ as regards acute alcoholism. Aside from these authors we know of no one who has studied the effect of drugs on the electro-encephalograms.

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1 Berger, Hans (a) Ueber das Elektrenkephalogramm des Menschen, *Arch f Psychiat* **87** 527, 1929, (b) *J f Psychol u Neurol* **40** 160 (May) 1930, (c) *Arch f Psychiat* **94** 16, 1931, (d) **97** 6, 1932, (e) **98** 231, 1932, (f) **99** 555, 1933, (g) **100** 301, 1933, (h) **101** 452, 1933, (i) **102** 538, 1934, (j) **103** 444, 1935, (k) **104** 678, 1936, (l) Ueber die Tätigkeit des menschlichen Grosshirns, *Munchen med Wchnschr* **80** 844 (June 2) 1933, (m) Das Elektrenkephalogramm des Menschen, *Med Welt* **7** 928 (July 1) 1933, (n) Das Elektrenkephalogramm des Menschen und seine Bedeutung für die Psychophysiologie, *Ztschr f Psychol* **126** 1, 1932.

2 Gibbs, F A, Davis, H, and Lennox, W G. The Electro-Encephalogram in Epilepsy and in Conditions of Impaired Consciousness, *Arch Neurol & Psychiat* **34** 1133 (Dec) 1935.

3 Loomis, A L, Harvey, E N, and Hobart, G. Electrical Potentials of Human Brain, *J Exper Psychol* **19** 249, 1936.

of human beings Various workers have, however, carried out experiments on animals which bear directly on this subject, notably Adrian,⁴ Bremer,⁵ Range⁶ and Derbyshire⁷ and their associates

In our experiments small metal electrodes were cemented to the scalp and to the lobe of the ear The electrode on the scalp was connected to the grid of a capacity-coupled vacuum tube amplifier having a gain of about ten million, the ear electrode was connected to ground Records were made on paper with an ink-writing oscillograph capable of registering frequencies up to 40 per second When it seemed of interest to compare the simultaneous activity from different parts of the head, additional electrodes were cemented to appropriate points on the scalp, and each was connected to the grid of an amplifier similar to the one just referred to The ear was used as a common ground for all channels of amplification Our equipment allowed the simultaneous recording of activity from four parts of the brain Control tracings were obtained for a period of from fifteen to thirty minutes before the drug was given, and the record was continued after the maximum clinical effect of the drug had been obtained Both normal subjects and patients were used The subject sat in a comfortable chair or lay in a hospital bed In all, eighty-four experiments were carried out with twenty drugs

In the normal waking subject the potentials which can be led off from the head have a voltage of from ten to seventy-five millionths of a volt or about one one hundredth of the voltage recorded in the electrocardiogram For purposes of orientation, figure 1 is shown This is a short segment of the record of a normal subject The most prominent rhythm is 10 a second, seen best in the occipital region and usually influenced greatly by the opening and closing of the eyes and by what, for want of a better term, must be called attention With the eyes closed, the 10 a second rhythm is prominent, with the eyes open, it temporarily disappears, and, in general, any concentration of attention tends to abolish this rhythm In some persons, however, the 10 a second rhythm does not appear at all, in others it continues even when the eyes are open Adrian⁸ and Jasper⁹ have shown that the pattern of the

4 Adrian, E D, and Matthews, B H C The Interpretation of Potential Waves in the Cortex, *J Physiol* **81** 440, 1934

5 Bremer, F Action des differents narcotiques sur les activités electriques spontanee et reflexe du cortex cerebral, *Compt rend Soc de biol* **121** 861, 1936

6 Range, R W Der Einfluss von Narkotika auf die Tätigkeit der Grosshirnrinde des Kaninchens, *J f Psychol u Neurol* **46** 364, 1935

7 Derbyshire, A J, Rempel, B, Forbes, A, and Lambert, E F The Effects of Anesthetics on Action Potentials in the Cerebral Cortex of the Cat, *Am J Physiol* **116** 577, 1936

8 Adrian, E D, and Yamagiwa, K Origin of Berger Rhythm, *Brain* **58** 323 (Sept) 1935

9 Jasper, H H, and Andrews, H L Human Brain Rhythms I Recording Technique and Preliminary Results, *J Gen Psychol* **14** 98, 1936

potential fluctuations differs for various areas of the cortex. The work of Hallowell Davis¹⁰ indicated that the pattern of any person, like his signature, is, within limits, characteristic and constant. Furthermore, the records of identical twins are similar, an observation which suggests an inherent biologic significance in the rhythms portrayed in the electro-encephalogram.

Any observed rhythm presumably represents the sum total of the changes of potential of various discharging units in the region of the brain beneath the stigmatic electrode. Certain procedures, such as opening the eyes or increasing the attention, cause a flattening of the waves, presumably by a "canceling out" process. In some conditions, such as death, deep asphyxia and postepileptic stupor, the flatness of the record undoubtedly represents a decrease in the total electrical activity of the

ELECTRO - ENCEPHALOGRAM NORMAL SUBJECT E L

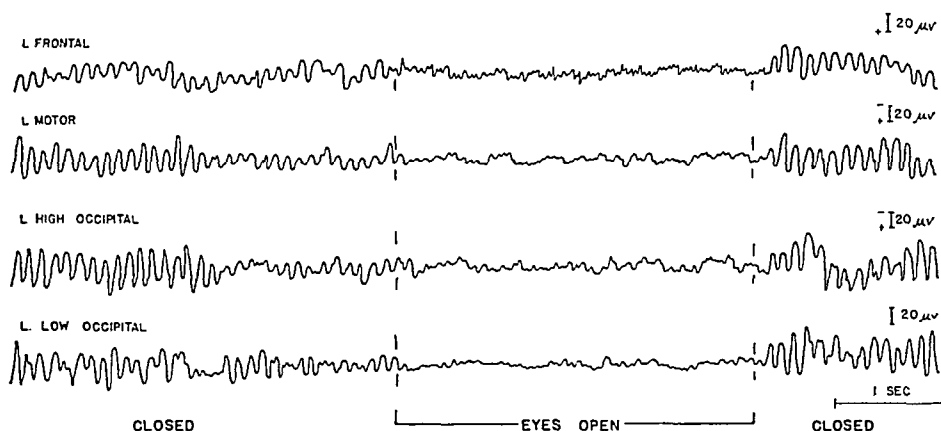


Fig 1—The electro-encephalogram of a normal subject with eyes closed and open. The four curves are simultaneous records of potential fluctuations from four different parts of the head, as labeled. The deflection caused by a signal of known sign and voltage is shown at the right of the figure. The speed of the paper is indicated by the one second time calibration in the lower right corner of the figure (also in figures 2 to 7). At the bottom of the chart are shown the periods during which the eyes of the subject were open and closed.

brain suggestive of a discharged battery. An increase in voltage may mean more units discharging synchronously or a greater discharge from each single unit, or both conditions may obtain. What these discharging units are is not known, but because the type of activity seen in the electro-encephalogram is best obtained from masses of gray substance, the assumption seems reasonable that the structures responsible are cell bodies or synapses.

10 Davis, H, and Davis, P. A. Action Potentials of the Brain in Normal Persons and in Normal States of Cerebral Activity, *Arch Neurol & Psychiat* 36 1214 (Dec) 1936

RESULTS

We shall first cite the results obtained with drugs the administration of which was followed by significant changes in the electro-encephalogram

Scopolamine—Scopolamine or atropine was given in three cases, in doses of from $\frac{1}{100}$ to $\frac{1}{50}$ grain (0.6 to 1.3 mg) intravenously. After the injection there was at first a decrease in the voltage of all waves (a change characteristic of drowsiness), and then bursts of regular waves of high voltage appeared with a frequency of about 10 a second. These bursts came rather regularly at about ten second intervals.

EFFECT OF SCOPOLAMINE

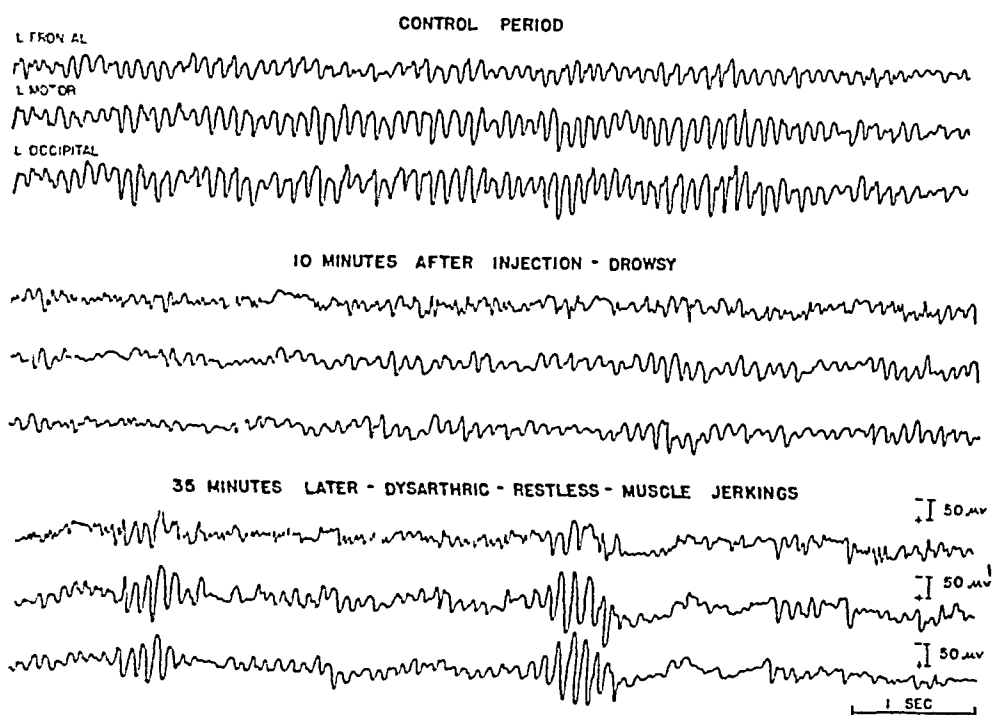


Fig 2—The effect of the intravenous injection of $\frac{1}{50}$ grain (1.3 mg) of scopolamine. Simultaneous tracings from three areas of the skull (left frontal, left motor and left occipital) are shown. The first trio of simultaneous curves was made in the control period before scopolamine was injected. The second trio was made ten minutes after the injection, when the patient was somewhat drowsy, the third trio was made thirty-five minutes later, when speech was disarticulate and the patient was having involuntary twittings of muscle groups every few seconds. The large, slow fluctuation in the last three records correlated with the involuntary muscular movements.

and lasted from one to three seconds. During this type of activity the patient was not asleep. In the experiment in which we gave a dose of scopolamine sufficient to produce muscular twitching ($\frac{1}{50}$ grain, 1.3 mg), the twitches coincided with unusually large bursts of these high voltage, 10 a second waves. Figure 2 is the record of this experiment.

Morphine—One-fourth grain (16 mg) of morphine sulfate was given intravenously to each of three subjects. As with scopolamine, the waves of the electro-encephalogram became somewhat flattened, and the record was interspersed with bursts of high potential, 10 a second waves. One epileptic patient regularly had, during sleep, abnormal sharp spikes in the record taken from the frontal area of the brain. Injection of morphine caused these abnormal spikes to appear (even though the patient was not asleep at the time).

Barbiturates¹¹ and Sodium Bromide—The effects of various barbiturates and sodium bromide on the normal electro-encephalogram were much alike. Soluble phenobarbital U S P (phenobarbital sodium) was given fourteen times (5 to 10 grains [0.3 to 0.6 Gm.] intravenously). When sleep or drowsiness was not induced, there was no detectable change in the normal electro-encephalogram. When the injection was followed by drowsiness, the record usually flattened as in natural drowsiness, if sleep occurred, the record closely resembled that obtained during normal sleep, that is, large, slow waves appeared, and a new frequency of approximately 14 per second (which is rare in waking states) appeared in bursts (fig. 3).

These statements are true also for sodium bromide, which was given intravenously to eight subjects, 30 grains (2 Gm.) to each. In the cases in which a maximum effect was shown, the slow waves became slower, and the bursts of fast activity became less numerous, that is, there was an exaggeration of the changes seen during sleep.

In addition to observations of persons with normal electro-encephalograms given phenobarbital and sodium bromide, we made them on patients having frequent abnormalities of rhythm, which we believe are diagnostic of epilepsy. Records depicting the effect of anticonvulsants on the wave formation which is typical of petit mal seizures have been published elsewhere.¹² Both these drugs acted either to prevent the appearance of abnormal rhythms or to disrupt and shorten them. Petit mal seizures, which before were visible to the observer, now were detectable only by the electro-encephalograph. One patient who showed abnormal waves during natural sleep had them also in even increased number during sleep induced by these anticonvulsant drugs.

¹¹ The phenobarbital, evipal (N-methylcyclohexenylmethylmalonylurea) and chemical homocamfin (methylisopropylcyclohexone) used in these studies were supplied by the Winthrop Chemical Company, the ergotomine tartrate was supplied by the Sandoz Chemical Works.

¹² Lennox, W. G., Gibbs, F. A., and Gibbs, E. L. Effect on the Electro-Encephalogram of Drugs and Conditions Which Influence Seizures, *Arch Neurol & Psychiat* 36:1236 (Dec.) 1936.

Evipal (N-methylcyclohexenylmethylmalonylurea) or pentobarbital sodium was given intravenously to six subjects in doses of from 2 to 8 grains (0.13 to 0.5 Gm). When the larger amounts were used, the injection was given slowly, the subject counting the while so that the various stages of anesthesia could be correlated with the pattern of the electro-encephalogram. With increasing drowsiness of the subject, the rhythm changed, until at the stage of surgical anesthesia the slow waves were at a frequency of only 1 or 2 a second and the 10 a second activity was represented only by the jagged, irregular contour of the slow waves. It should be pointed out, however, that in the early stages of anesthesia, while the patient was still sufficiently conscious to count

EFFECT OF SLEEP AND VARIOUS SEDATIVES
(ELECTRODE OVER L MOTOR AREA OF PATIENT W.C.)

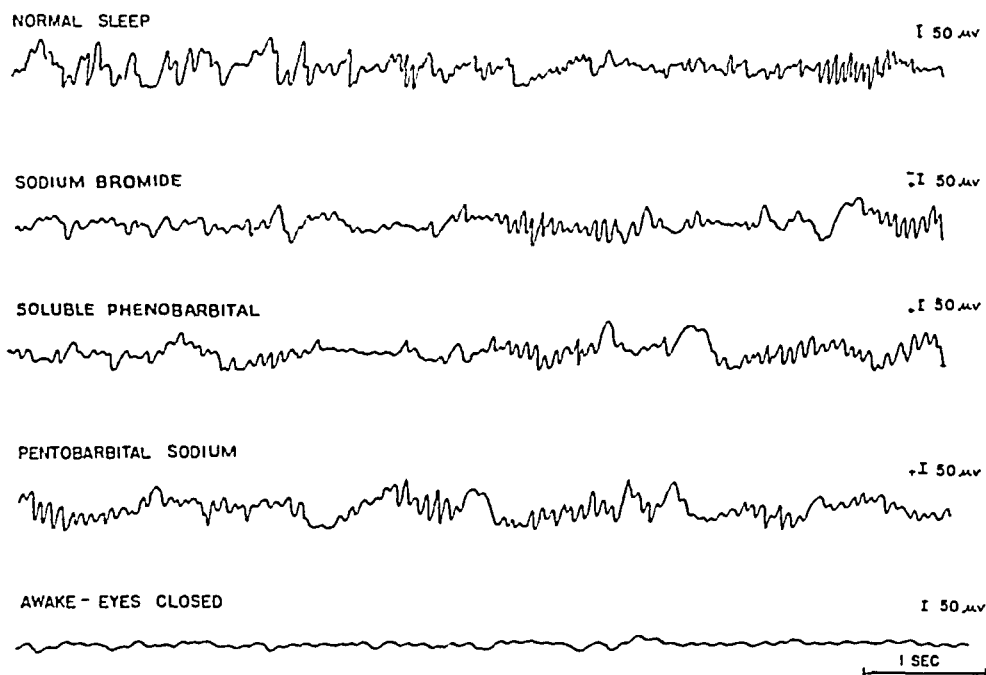


Fig 3—The effect of sleep and of various sedatives given on different occasions to the same subject. The curve at the bottom of the chart was a control record with the patient awake and the eyes closed. The record at the top was made when the patient was soundly asleep. The three remaining records were made after the intravenous injection of 30 grains (2 Gm) of sodium bromide, 10 grains (0.65 Gm) of soluble phenobarbital U S P (phenobarbital sodium) and 4 grains (0.26 Gm) of pentobarbital sodium, respectively. In each instance the patient was asleep. The similarity of the records of induced and of natural sleep is obvious.

(fig 4), there was a great increase in the voltage of all the components of the normal electro-encephalogram. This increase in voltage persisted but became intermittent as unconsciousness supervened, i e., the steady

high voltage was broken up into buists of activity. These buists became farther and farther apart as the anesthesia progressed, and large, slow waves, about 1 or 2 per second, appeared.

When doses are used that are just sufficient to induce sleep, the curve may be indistinguishable from the person's record during ordinary sleep. The various sedatives which we have used all produce comparable changes in the electrical activity of the cortex. Figure 3 is the record of a subject who was given intravenous injections of various sedatives on different occasions. At the bottom is a sample of his waking record. The similarity is obvious between this patient's record taken during ordinary sleep and the record taken during sleep which followed the intravenous injection of a sedative.

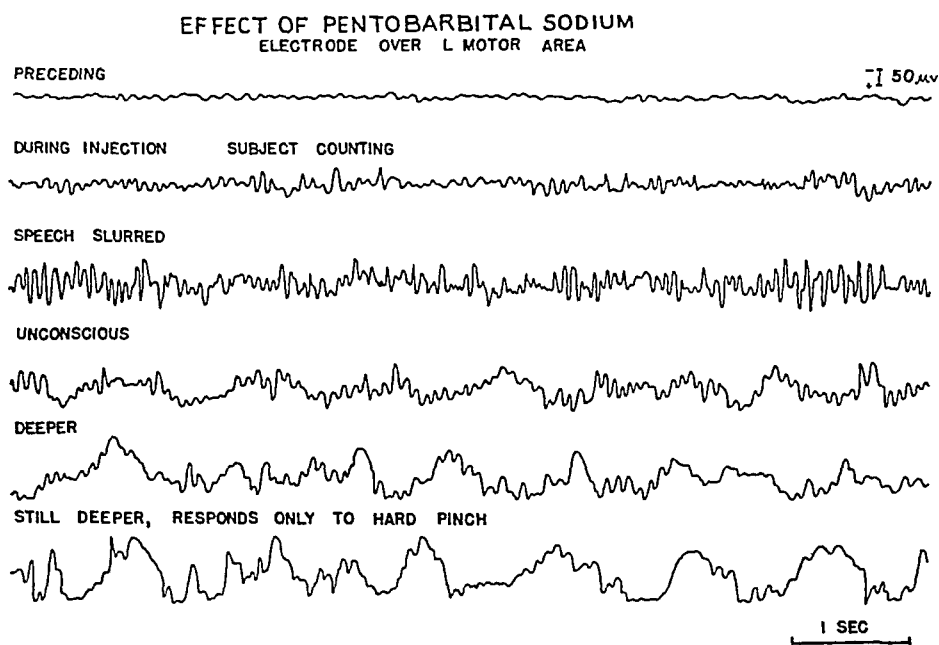


Fig 4—The effect of intravenous injection of pentobarbital sodium. All the records in this figure were from the left motor area. The top strip was made during a normal control period before an injection was given. Subsequent strips were taken at various intervals during and after the injection. The second and third strips were made when the patient was counting, and the fourth strip was made when he had ceased to count and did not respond to questions. The bottom strip is from the record made when he was in a state of light surgical anesthesia, responding only to painful stimuli.

Ether and Alcohol—Anesthetization by inhalation of ether was produced in three subjects, and mild intoxication with alcohol (induced by the ingestion of 30 or 40 cc of 95 per cent alcohol) was studied in three subjects. One intoxicated person was secured from the accident ward. A study of the records obtained from intoxicated patients indicates that ether and alcohol produce changes in the electro-encephalogram.

which are altogether comparable. These changes have a general similarity also to those produced by the barbiturates and by anesthesia induced by pentobarbital and evipal, though there are certain characteristic differences. The barbiturates in soporific doses may produce at first flattening as in natural drowsiness and then a great increase in the voltage of those frequencies, which are around 14 per second, the first effect of alcohol and ether, on the other hand, is to increase the voltage of those frequencies which are around 20 per second and at the same time to diminish the voltage of frequencies around 10 per second. This occurs while the subject is still conscious. As consciousness is lost, these high voltage, fast waves disappear and high voltage, slow waves with a frequency of about 5 per second take their place. As unconsciousness becomes more and more profound, the slow waves become slower and slower. In ether anesthesia when a "surgical level" is reached, the slow waves have a frequency of about 1 per second (fig. 5). Superimposed on these are small, faster waves with a frequency of 10 or 20 per second, so that the slow waves have a cretated appearance. A practical application of these observations might be the use of the electro-encephalogram as a measure of the depth of anesthesia during surgical operations. The anesthetist and surgeon could have before them on tape or screen a continuous record of the electrical activity of both heart and brain.

A somewhat similar sequence of events is present in alcohol intoxication. The first record in figure 6 was taken when the patient was "dead drunk," unresponsive to any but painful stimuli. The second tracing is representative of the record taken ten hours later, when he was awake and able to talk intelligibly, but his manner and his sullen, suspicious attitude were abnormal. The third tracing was made seven hours later, when he appeared normal. As with ether, the largest waves (with 10 or 20 per second waves still visible) came with deepest unconsciousness.

COMMENT

Our findings are in general in accord with those of other workers who have studied the effect of the same drugs. Berger¹⁰ studied morphine and the barbiturates particularly. At no point do we disagree with his findings. The report of Loomis, Harvey, and Hobart on a case of acute alcoholism differs from ours by its failure to mention the presence of large, slow waves. Adrian's⁴ records of ether anesthesia in animals are similar to ours, as are those of Biemer⁵ and Derbyshire, Rempel, Forbes and Lambert⁷ on the effect of ether and the barbiturates on animals. Range⁶ also worked with ether on animals and reported the same type of alteration that we have described.

EFFECT OF ETHER ELECTRODE OVER L MOTOR AREA

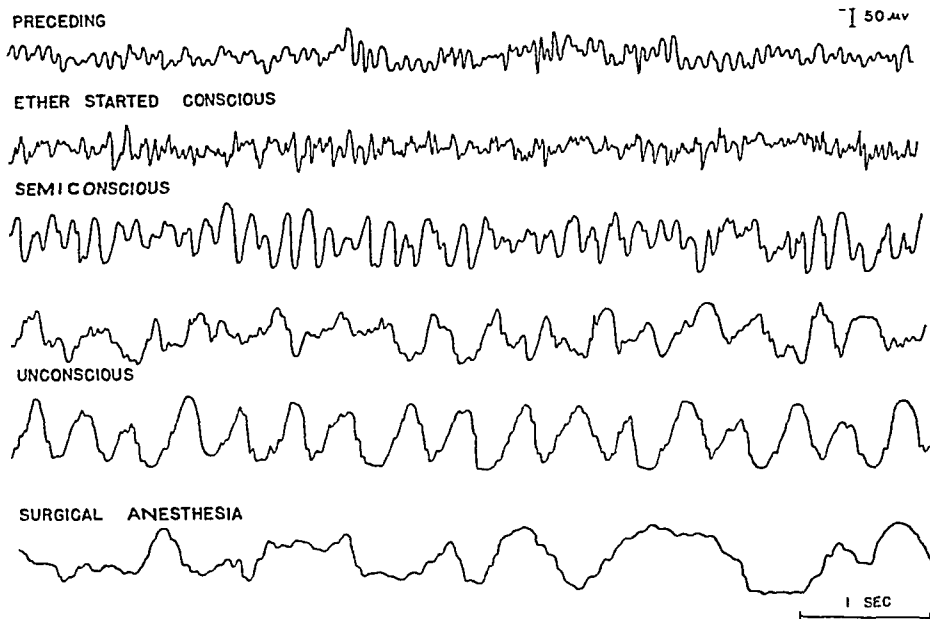


Fig 5—A record made during inhalation of ether. As in the preceding figure, the electrode was over the left motor area. The top strip was made when the patient was awake with eyes closed, the second shows the change that occurred when etherization was started but while the patient was fully conscious. In the third and fourth strips consciousness was progressively lessened and in the fifth the patient was unconscious. In the bottom strip he was in a state of surgical anesthesia, not responding to painful stimuli.

EFFECT OF ALCOHOLIC INTOXICATION PATIENT J C

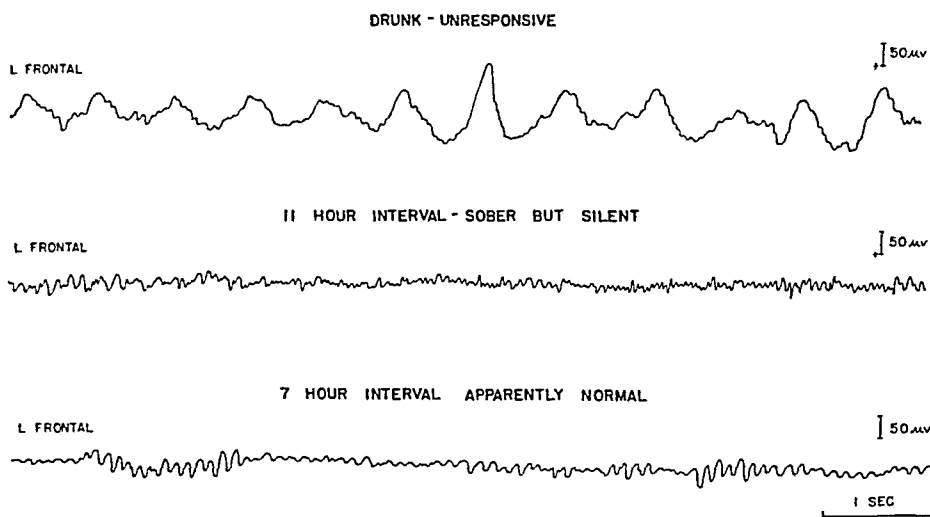


Fig 6—The effect of alcohol intoxication. In this instance the first strip was taken from a record made when the patient was drunk and unresponsive to any but painful stimuli. The middle strip is from a record taken eleven hours later, when he could be called sober but when he was unnaturally silent and morose. The bottom strip shows the change that had occurred seven hours later, when the patient was normal.

A number of drugs which we tried did not have any appreciable effect on the electro-encephalogram, at least in the doses given. The following list of these drugs gives the doses used and the number of experiments. Administration was by the intravenous route, except that sodium nitrite was given by mouth, pitressin intramuscularly and trichlorethylene by inhalation.

Obviously, for conclusive demonstration the number of observations with some of the drugs in this list would need to be increased.

The presence of strychnine in this group may seem strange in view of the animal experiments of Fischer¹³ and of Kornmüller,¹⁴ in which increased electrical activity was recorded after the administration of strychnine. However, these experimenters used amounts of strychnine sufficient or nearly sufficient to induce convulsions. We used only $\frac{1}{60}$ to $\frac{1}{10}$ gram (1 to 6 mg) intravenously, an amount insufficient to induce motor symptoms.

	Dose	No of Experiments
Epinephrine hydrochloride	0.5 to 0.8 mg	6
Benzedrine sulfate	10 mg	3
Caffeine with sodium benzoate	0.5 Gm	3
Cibalgin (aminopyrine and dial)	0.25 Gm	3
Cobra venom	1 cc	1
Ergotamine tartrate	0.5 mg	6
Histamine	0.5 cc	2
Pitressin (after 2 liters of water)	1 cc	2
Sodium nitrite	0.3 to 0.5 Gm	2
Strychnine sulfate	1 to 10 mg	6
Trichlorethylene	1 cc	1

In five of the eight instances in which ergotamine tartrate was used, the subjects were experiencing migraine headache, which was completely relieved by the injection. Two of these electro-encephalographic records showed significant changes. We intend to pursue this subject further.

Explanation is needed also regarding our negative results with camphor. Amounts insufficient to produce symptoms did not alter the rhythm, but in four instances an intravenous dose (0.5 to 1 cc) of a preparation of camphor, homocamfin (methylisopropylcyclohexone), given to a patient with epilepsy was followed by a generalized convulsion. Approximately twenty seconds after the homocamfin was injected, the voltage of the waves became greater. Parenthetically, this method affords a means of measuring circulation time from the vein of the arm to the cortical cells of the brain. The potentials continued to

13 Fischer, M. H. *Elektrobiologische Auswirkungen von Krampfgiften am Zentralnervensystem*, Med. Klin. **29** 15, 1933.

14 Kornmüller, A. E. *Der Mechanismus des epileptischen Anfalles auf Grund bioelektrischer Untersuchungen am Zentralnervensystem*, Fortschr. d. Neurol., Psychiat. **7** 391 (Sept.), 414 (Oct) 1935.

increase in voltage (though without clinical evidence of seizure) until finally, after a lapse of about thirty seconds, the patient had a psychomotor attack (fig 7) It seems probable that any drug capable of producing convulsions, if given in a convulsing dose, will cause disturbances in the normal electrical activity of the brain comparable to the disturbances seen when a spontaneous epileptic seizure is recorded

Probably a similar statement applies to drugs capable of producing sleep Marked variations from the normal electro-encephalographic tracing are seen only in association with convulsions (or involuntary movements), sleep or stupor Gross alterations of the electro-encephalogram likewise are seen after the administration of only those drugs which produce convulsions (involuntary movements), sleep or stupor,

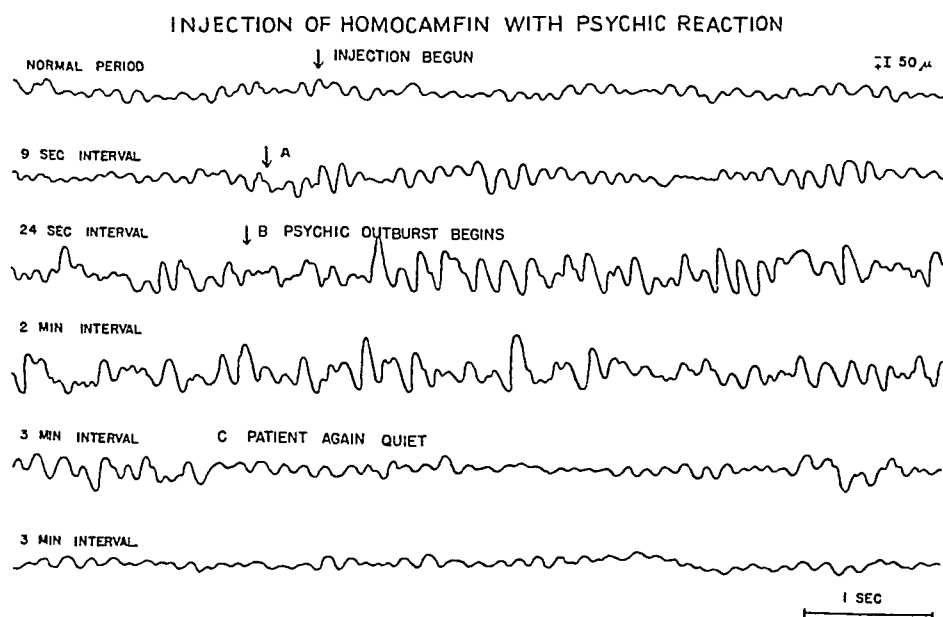


Fig 7—The effect of an intravenous injection of 1 cc of homocamfin The top strip is from the patient's normal record with eyes closed Intravenous injection of the drug was begun at the point marked by the arrow A nine second interval separated the first and second strips At the arrow marked *A*, which indicates a point sixteen seconds after the injection was started, the first effect of the drug on the potentials can be noted At *B* in the third curve, which indicates a point forty-seven seconds after the beginning of the injection, the subject began to have a mild psychic outburst, which continued for a little more than five minutes During this period he was emotionally disturbed and did not reply to questions, he had no recollection of what took place after the episode was over At the point marked *C* on the fifth curve he was again quiet and able to answer questions

and these alterations do not occur unless a sufficient dose is given to produce one of these effects In comparing two drugs we have found, in general, that the more nearly alike the effect of the drugs on the

involuntary muscular activity or on the consciousness of the patient, the more nearly alike the records obtained with the electro-encephalograph

Aside from the effect of medication on the normal electro-encephalogram, we have observed the effect of certain procedures (inhalation of carbon dioxide and concentration of attention) which tend to alter both the normal rhythm and the rhythm in epilepsy and which inhibit seizures. These results have been presented elsewhere¹⁰

In the present stage of study of the electrical activity of the brain we are primarily concerned with the securing of data, which must precede any attempt at interpretation of results. The administration of drugs which affect mainly the vegetative system (ergot, epinephrine and atropine) had little appreciable effect on the electrical activity of the cortex. When drugs were used which did alter the electrical activity of the cortex, the activity of all regions from which we led off was modified. It is possible that careful study might show that changes developed in one area before they did in another or that alterations were greater in a certain area. These are questions that can be adequately dealt with only if the investigation is not limited to the outer surface of the cortex but includes the deeper-lying gray masses, particularly the diencephalon. A discussion of the possible meaning of alterations such as those which we have described is outside the scope of the present paper and will be dealt with elsewhere in conjunction with the interpretation of our findings in epilepsy.

SUMMARY

Observations on human beings have been made of the effect on the electro-encephalogram of twenty drugs known to affect the central nervous system. The most definite changes attend the use in effective doses of convulsants, sedatives and anesthetics. Drugs primarily affecting the autonomic nervous system produce no comparable changes.

Sedatives cause changes similar to those observed in normal sleep. In place of the fast and rather steady activity characteristic of the waking state, there are slow, large voltage fluctuations, with occasional bursts of fast activity and also short periods in which there are almost no fluctuations. If sedation is so heavy that the patient cannot be aroused, the bursts of fast activity disappear, and the slow components become slower, of larger voltage and almost continuous. Ether produces, first, a decreased voltage of the lower frequencies in the normal record and an increased voltage of the higher frequencies and, later, large voltage, slow waves with a 10 a second rhythm superimposed. Electro-encephalography may therefore be of value in controlling depth of anesthesia and sedation. Alcohol is similar in its effect to ether.

Convulsants produce large voltage disturbances such as are seen in epileptic seizures, the frequency may be fast or slow. In patients having frequent petit mal seizures, bromide or phenobarbital in doses insufficient to change normal electrical activity prevents or disorganizes the pattern of the discharges which characterize the seizure.

CONCLUSIONS

Only those drugs which were given in sufficiently large doses to cause impairment of consciousness or involuntary muscular movements produced marked alterations in the electro-encephalogram.

Drugs which cause a sleeplike state altered the electro-encephalogram in the same general way as natural sleep.

Drugs which cause a profound abolition of consciousness produced records similar to those seen in stupor from whatever cause.

Drugs which cause convulsions resulted in alterations of electrical activity similar to those which occur in the convulsions of epilepsy.

The more nearly alike the clinical action of two drugs, the more nearly alike are the changes which they produce in electro-encephalograms.

Progress in Internal Medicine

BRIGHT'S DISEASE

A REVIEW OF RECENT LITERATURE

WILLIAM S McCANN, M D

ROCHESTER, N Y

EXPERIMENTAL GLOMERULONEPHRITIS

The past year has been characterized by marked progress in attempts to produce glomerulonephritis experimentally. These attempts have been recently reviewed by Masugi,¹ who was one of the earliest to achieve experimental glomerulonephritis, by Ahlstrom,² and by Smadel.³ All of these workers have utilized cytotoxic serum in its production.

Ahlstrom² began by investigating the action of Dick toxin, finding that it had a weak nephrotoxic action and produced only a few focal degenerative changes when injected into the renal arteries of normal rabbits or of rabbits which had been previously sensitized to Dick toxin.

Ahlstrom found also that when serum was injected into the renal arteries of sensitized animals most of them showed only perivascular cell infiltrates, frequently localized about the afferent glomerular artery, in which occasionally hyaline thrombi were observed and in some instances slight glomerular changes as well. When, however, animals which had been sensitized to horse serum were given preliminary injections of a staphylococcus toxin, subsequent injections of serum gave a different result. The changes which then ensued were notably glomerular and appeared in the form of an intracapillary reaction. It is also noteworthy that in some animals so treated thrombi of fibrin were found in the capillaries of the liver, with acinar necrosis and bleeding, suggestive of the hepatic lesions of eclampsia of pregnancy. These experiments led

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1 Masugi, M. Die Pathogenese der diffusen Glomerulonephritis im Lichte experimenteller Erzeugung dieser Nierenerkrankung bei Tieren, *Zentralbl f inn. Med* **56** 417 (May 11) 1935.

2 Ahlstrom, C G. Zur Pathogenese der akuten diffusen Glomerulonephritis. Experimentelle Untersuchung uber die allergische Gewebsreaktion der Niere, *Acta path et microbiol Scandinav*, supp 29, 1936, p 1.

3 Parks, A E, and Taussig, B L. Reaction of Sensitized Dog's Kidney to Horse Serum Injected into Renal Artery, *Proc Soc Exper Biol & Med* **34** 889 (June) 1936.

Ahlstrom to conclude that in order to produce glomerulonephritis experimentally it is necessary to have both a general allergic hypersusceptibility and an organ-predisposing factor. His failure to produce significant lesions in sensitized animals by the injection of horse serum alone is borne out by similar experiments by Parks and Taussig.³

Smadel⁴ has made extremely important observations on the production of nephritis experimentally with nephrotoxic serum. In producing the serum he found that even with careful preliminary perfusion of the antigenic kidney the resulting serum contained substances other than pure renal cytotoxins. Pure nephrotoxic effects were produced in rats only when other antibodies had been absorbed from the serum and when the rats had been desensitized to the antirat serum of rabbits. The pure nephrotoxic effects consisted of proteinuria and cylindruria, azotemia and anasarca but no hematuria. Hematuria and associated glomerular changes occurred when anaphylactoid factors were present and did not occur if these factors were absorbed or if the animals were desensitized.

Smadel found the nephrotoxic factor to be absorbed by renal cells, by fat-free renal substance and to some extent by hepatic cells and fat-free hepatic substance. It was not absorbed by lipids from the kidney, liver or brain or by red blood corpuscles or serum. It was all found to be present in the globulin fraction of the serum. Such serum is relatively organ specific. Smadel finds it difficult to desensitize against the nephrotoxic factor so as to produce reverse anaphylaxis.

The course of the experimental nephritis thus induced has been studied by Farr and Smadel,⁵ who have devised ingenious methods for obtaining blood from rats and for collecting urine from them for determination of the urea clearance. Farr has previously described micromethods for the determination of urea and ammonia. By these methods they have established the normal values of urea clearance for rats.

NEPHRITIC HYPERTENSION

Interest seems to have been renewed in vasopressor substances arising in the kidney or in pressor effects originating in those organs. Govaerts and Dicker⁶ report the finding of a vasopressor substance

4 Smadel, J. E. Experimental Nephritis in Rats Induced by Injection of Anti-Kidney Serum, *J. Exper. Med.* **64** 921 (Dec.) 1936.

5 Farr, L. E., and Smadel, J. E. The Urea Clearance of Rats. Its Technique and Normal Range, *Am. J. Physiol.* **116** 349 (July) 1936.

6 Govaerts, P., and Dicker, E. Production intrarénale de substances hypertensives par ligature ou pincement de l'artère rénale, *Compt. rend. Soc. de biol.* **122** 809, 1936, Les substances vasopressives présentes dans le sérum des néphrétiques hypertendus existent-elles dans le sérum des sujets normaux? *ibid.* **122** 807, 1936.

in the kidney of a dog when the renal artery was partly closed with a clamp. In such a case alcoholic extracts of the animal's blood and of the partly ischemic kidney exerted a strong vasopressor effect on other dogs. When the artery to one kidney was kept ligated for several days, the pressor substance was found within that kidney, though none was found in the blood or in the other kidney.

That the mechanism of pressor effects from the injured kidney is not entirely humoral is shown by the studies of Arnott, Kellar and Matthew.⁷ These authors observed that hypertension did not occur in oxalate nephritis if the kidneys were denervated, though it does occur if the nerves are intact. Injections of oxalate did not cause hypertension in nephrectomized animals. When unilateral nephrectomy was performed and the other kidney was denervated, hypertension did not follow the injection of oxalate. The authors point out, however, that the injury to the kidneys that is due to the oxalate is purely tubular. They report preliminary experiments on rabbits with experimental glomerulonephritis produced by a nephrotoxic duck serum. So far hypertension has not been observed in animals subjected to unilateral nephrectomy and denervation of the other kidney.

TOXEMIA OF PREGNANCY

Peters,⁸ after a review of a considerable number of cases of toxemia of pregnancy, expresses the belief that "toxemia" does not occur *de novo* but represents an explosive reaction induced by pregnancy in women who have suffered from previous renal or vascular injury, such as pyelitis, pyelonephritis, nephritis or hypertension—in fact, any of the diseases which, outside of pregnancy, give rise to arteriolar disease, hypertension or functional impairment of the kidneys.

Peters has been unable to find any fundamental disorder of metabolism underlying toxemia of pregnancy. Studies of blood chemistry or metabolism have thrown surprisingly little light on the subject. Peters believes that during pregnancy preexisting renal or vascular disorders of a benign nature may suddenly burst into a malignant state. Since the frequency of toxemia exceeds greatly the incidence of renal and vascular disease in nonpregnant women of comparable age, one must assume that the gravid state increases the sensitivity of the kidneys and vascular system to the action of the ultimate etiologic agents.

⁷ Arnott, W. M., Kellar, R. J., and Matthew, G. D. The Experimental Pathology of Renal Hypertension, *Edinburgh M. J.* **43** 135 (Sept.) 1936.

⁸ Peters, J. P., and Zimmerman, H. M. The Role of Pyelitis in the Production of Toxemias of Pregnancy, *Tr. A. Am. Physicians* **51** 287, 1936. Peters, J. P., Laviertes, P. H., and Zimmerman, H. M. Pyelitis in the Toxemias of Pregnancy, *Am. J. Obst. & Gynec.* **32** 911 (Dec.) 1936. Peters, J. P. The Nature of Eclampsia, *Yale J. Biol. & Med.* **9** 233 (Jan.) 1937, Toxemias of Pregnancy, *ibid.* **9** 311 (March) 1937.

Peters dismisses pituitary basophilia as a causative factor in toxemia of pregnancy since it is found in patients with hypertension from a variety of causes, hence it may be regarded simply as a mechanism by means of which the organism raises the blood pressure in response to a variety of impulses. Whether or not Peters is justified in such a summary dismissal of this factor, he has at least directed thought and inquiry concerning toxemia along new lines. If his views prove ultimately to be correct, he will have raised new issues concerning the prevention of toxemia of pregnancy.

PROTEINURIA

Bing⁹ has prepared an excellent historical review of both early and recent work concerning the origin of the urinary proteins. Using creatinine clearance as a relative measure of the rate of glomerular filtration, he finds that the total protein and the albumin content of the urine vary with the creatinine clearance. He finds that the ratio of the protein content of the urine to the creatinine concentration index has a constant value under constant experimental conditions in a given patient, though the values vary for different persons, since they must depend on individual filtration values and on the state of permeability of the glomerular membrane. Parallelism was also found to exist between urea excretion and proteinuria and to some extent cholesteroluria. He observed, as others have also, that proteinuria generally increases in persons on high protein diets. The latter observations led him to the conclusion that the change in protein content of the diet in some way alters the permeability of the glomeruli, a somewhat questionable conclusion, since it leaves out of account the probable changes in renal blood flow.

Since Bing finds evidence that the tubules function perfectly in nephrosis, he renews the suggestion, previously made by others, that the histologic appearances of the renal tubules, which are conventionally described as "degenerative changes," are simply due to the presence of small quantities of protein (and lipoids) which have made their way into the tubular cells during protracted periods of a high degree of proteinuria.

SERUM PROTEIN

Two recent studies have been concerned with the nature of the serum protein in nephrosis. Goettsch and Reeves¹⁰ prepared precipitins for the protein of normal serum, which precipitate protein almost

⁹ Bing, J. Studies on Proteinuria, "Albuminuria," *Acta med Scandinav*, supp 76, 1936, p 1.

¹⁰ Goettsch, E, and Reeves, E. B. Observations on the Nature of Serum Proteins in Nephrosis, *J Clin Investigation* 15 173 (March) 1936.

quantitatively from such serum. When these precipitins were applied to serum of patients with nephrosis, both the albumin and the globulin fraction failed to precipitate completely. While the patient was convalescing from nephrosis the protein of the serum resumed its normal relation to precipitins.

In acute hemorrhagic nephritis the serum protein was precipitated in a normal manner.

Goettsch and Reeves also used globulin from serum of nephrotic subjects to stimulate antibody formation in rabbits. The antiserum thus formed was found to be not identical with that formed against the globulin from normal serum.

Alving and Mirsky¹¹ have also found that the albumin fractions of the blood and urine of nephrotic subjects differ from normal. When the globulin fraction was precipitated the remaining protein was found to consist in part of normal serum albumin and in part of a protein which contained far less cystine than the albumin of normal serum. On the other hand, when the urinary globulin was precipitated the remaining protein contained more cystine than the corresponding fraction in the plasma of nephrotic subjects but less than normal serum albumin. From this the authors conclude that the plasma albumin in nephrosis contains a substance with a low cystine content which passes through the kidney less readily than does normal serum albumin.

Wies and Peters¹² have reexamined the relation of serum protein to osmotic pressure and by statistical methods have derived equations for prediction of osmotic pressure from the protein analyses. They have found that the factors for albumin and globulin are of the same order of magnitude as those determined by Govaerts and von Farkas. They are not, however, proportionate to the commonly accepted values for the molecular weights of these proteins. Wies and Peters believe that calculations of the osmotic pressure from reliable analytic data are as likely to be accurate as attempts to measure it directly. Their data do not include any for patients with a high globulin (chiefly γ -globulin) value, such as is found in association with myeloma and lymphosarcoma, so that their formulas should not be applied in cases of these conditions.

PLASMA LIPIDS

Page, Kirk and Van Slyke¹³ have studied the plasma lipids in the chronic active stage of hemorrhagic Bright's disease, in which the

11 Alving, A. S., and Mirsky, A. E. The Nature of the Plasma and Urinary Proteins in Nephrosis, *J. Clin. Investigation* **15** 215 (March) 1936.

12 Wies, C. H., and Peters, J. P. The Osmotic Pressure of Proteins in Whole Serum, *J. Clin. Investigation* **16** 93 (Jan.) 1937.

13 Page, I. H., Kirk, E., and Van Slyke, D. D. Plasma Lipids in Hemorrhagic Nephritis, *J. Clin. Investigation* **15** 101 (Jan.) 1936.

urea clearance is above 20 per cent. In seven cases there was a definite tendency to hyperlipemia. As the disease passes into its terminal stages, it was found, there is a tendency for the level of the plasma lipids to decrease and it may fall below the normal limits. The values for individual lipids, free cholesterol, cholesterol esters and phosphatides rise and fall together.

A similar study was carried out by these same investigators¹⁴ for sixteen patients with uncomplicated essential hypertension, for none of whom the values for total plasma lipid or for any fraction of the lipid were in the least abnormal. These authors review the current ideas of the relation of hypercholesteremia to atheromatosis and hypertension, beginning with the work of Le Moine in 1911, which has met with varying support and denial by various investigators. In view of the negative findings of Page, Kirk and Van Slyke it appears that hypercholesteremia and elevation of the cholesterol-phosphatide ratio have nothing to do with arterial degeneration occurring in essential hypertension.

Page and Farr¹⁵ have investigated the effects of diet and of the administration of thyroid on the lipids of the blood in nephrosis. The hyperlipemia of nephrosis and of chronic active glomerulonephritis is not influenced by the amount of fat in the diet or by the administration of thyroid. Whatever value thyroid may have in nephrotic states, its effects are not dependent on changes in the plasma lipids, and a high value for these substances should not be taken as a contraindication to liberal use of fat in the diet.

In contrast to the hyperlipemia accompanying the hypoproteinemia of nephrosis is the absence of hyperlipemia in states of malnutrition. Man and Gildea¹⁶ report hypocholesteremia in such cases, usually associated with low values for total protein and albumin.

CLEARANCE TESTS IN RELATION TO GLOMERULAR FILTRATION AND RENAL BLOOD FLOW

In 1934 Van Slyke, Rhoads, Hiller and Alving¹⁷ studied the relation of urea clearance and renal blood flow estimated from samples of blood

14 Page, I. H., Kirk, E., and Van Slyke, D. D. Plasma Lipids in Essential Hypertension, *J. Clin. Investigation* **15** 109 (Jan.) 1936.

15 Page, I. H., and Farr, L. E. The Influence of High and Low Fat Diets and Thyroid Substance on the Plasma Lipids of Nephrotic Patients, *J. Clin. Investigation* **15** 181 (March) 1936.

16 Man, E. B., and Gildea, E. F. Serum Lipoids in Malnutrition, *J. Clin. Investigation* **15** 203 (March) 1936.

17 Van Slyke, D. D., Rhoads, C. P., Hiller, A., and Alving, A. The Relationship of the Urea Clearance to the Renal Blood Flow, *Am. J. Physiol.* **110** 387 (Dec.) 1934.

drawn directly from the renal vessels and demonstrated a marked parallelism between them. They found that dogs have a lower urea clearance when on low than when on high protein diets. This same effect of dietary protein on the urea clearance was observed by Farr¹⁸ in a study of four children with nephrosis. The increase in clearance is due not to urea but to some other factor which probably increases the renal blood flow. Farr also noted that the creatinine clearance of these patients behaved in a similar manner.

The use of the creatinine clearance as a measure of the rate of glomerular filtration was first proposed by Rehberg. More recently the clearances of other substances, such as inulin and xylose, have been studied. Shannon and Smith¹⁹ present the reasons for believing that no tubular activity is concerned in the excretion of inulin. They believe that xylose and sucrose are reabsorbed to some extent. The inulin clearance exceeds that of xylose by 22 per cent. When phlorizin is given, the disparity between the values does not exceed 10 per cent. Shannon and Smith suggest the use of inulin as a measure of glomerular filtration, though they do not regard it as finally proved that inulin is not resorbed. Shannon²⁰ has found that when the value for creatinine in the plasma is low the ratio of creatinine clearance to inulin clearance is 1.39, when the value for plasma creatinine is high the ratio is 1.12. These findings strongly support the belief that the excretion of creatinine may be influenced by tubular activity.

Simultaneous comparisons have been made by Landis, Elsom, Bott and Shiels²¹ of the clearances of creatinine and certain organic compounds of iodine, skiodan, diodrast and hippuran. They found that the clearances of creatinine and skiodan were of the same order of magnitude. The clearances of diodrast and hippuran were greater than the creatinine clearance. In renal insufficiency hippuran clearance is reduced proportionately to the urea and creatinine clearances.

The excretion of phenolsulfonphthalein (phenol red) has been studied by Goldring, Clarke and Smith²². In normal men the phenolsulfonphthalein clearance is considerably larger than that of inulin, being

18 Farr, L. E. The Effect of Dietary Protein on the Urea Clearance of Children with Nephrosis, *J Clin Investigation* **15** 703 (Nov.) 1936

19 Shannon, J. A., and Smith, H. W. The Excretion of Inulin, Xylose and Urea by Normal and Phlorizinized Man, *J Clin Investigation* **14** 393 (July) 1935

20 Shannon, J. A. The Renal Excretion of Creatinine in Man, *J Clin Investigation* **14** 403 (July) 1935

21 Landis, E. M., Elsom, K. A., Bott, P. A., and Shiels, E. H. Simultaneous Plasma Clearances of Creatinine and Certain Organic Compounds of Iodine in Relation to Human Kidney Function, *J Clin Investigation* **15** 397 (July) 1936

22 Goldring, W., Clarke, R. W., and Smith, H. W. The Phenol Red Clearance in Normal Man, *J Clin Investigation* **15** 221 (March) 1936

somewhat over three times as large with concentrations of dye in the plasma of less than 1 mg per hundred cubic centimeters. Most of the phenolsulfonphthalein in the plasma is bound by protein. The fraction which is free varies directly with the total concentration of the dye. These authors estimate that not more than 6 per cent of the dye is excreted by glomerular filtration. Values for the phenolsulfonphthalein clearance are of the general magnitude of 400 cc per minute of plasma and about 700 cc per minute of whole blood. The authors point out that this corresponds well with the renal blood flow estimated from the normal urea clearance (about 75 cc), which Van Slyke, Rhoads, Hiller and Alving²³ found to be about 10 per cent of the renal blood flow. Studies such as these inevitably revive interest in the possibilities of secretory activity of the tubules.

AGLOMERULAR TUBULES

In a previous review reference was made to the finding of aglomerular nephrons in contracted kidneys by Oliver and Luey, who speculated on the possibility of function in these tubular remnants kept alive by a blood supply from the vessels of Ludwig. In the course of a study of the vascular and parenchymal changes in the arteriosclerotic kidney Loomis²⁴ found adaptive changes in the vessels of Ludwig which bring them into great prominence as compared with their inconspicuousness in the normal kidney. Through such a vascular supply some tubules are preserved after occlusion of their glomerular supply, and in some cases tubular hypertrophy is noted. MacNider²⁵ also has drawn attention to aglomerular tubules in the kidneys of dogs with chronic renal disease produced by uranium. Long after the uranium injury the process of fibrosis and repair frequently obliterates glomeruli, yet tubules persist in a modified form, resembling those of the toadfish. MacNider suggests that the process of repair following degeneration is a reversion back to a type of structure normal for a remote ancestral form of kidney. It seems reasonable to believe that these well vascularized tubules are not without function, which in the severely damaged kidney may be of considerable importance.

23 Van Slyke, D. D., Rhoads, C. P., Hiller, A., and Alving, A. S. Relationships Between Urea Excretion, Renal Blood Flow, Renal Oxygen Consumption, and Diuresis. The Mechanism of Urea Excretion, *Am J Physiol* **109** 336 (Aug.) 1934.

24 Loomis, Dorothy. Plastic Studies in Abnormal Renal Architecture. IV. Vascular and Parenchymal Changes in Arteriosclerotic Bright's Disease, *Arch Path* **22** 435 (Oct.) 1936.

25 MacNider, W. deB. Pathological Changes in the Dog Kidney Resembling Normal Histological Structure in the Aglomerular Fish Kidney, *Opsanus Tau*, *Proc Soc Exper Biol & Med* **31** 293 (Nov.) 1933.

RENAL RICKETS

Pappenheimer²⁶ reports that in young rats a reduction in amount of renal tissue regularly results in an increase in size of the parathyroid glands. When partially nephrectomized rats were maintained on a diet poor in calcium, growth was stunted, and the resulting skeletal changes were of far greater severity than those produced by the diet alone. The resulting changes corresponded closely to those of severe renal rickets in children. The animals showed hyperphosphatemia and azotemia as in human beings with this disease.

MISCELLANEOUS REPORTS

Golding and Graef²⁷ report observations made on two of three patients who died after the transfusion of incompatible blood. The kidneys showed a necrotizing process in the tubules resembling that seen in mercurial nephrosis. Pigment casts were conspicuous. There was considerable interstitial edema of the kidneys, which were large.

Schmitker and Richter²⁸ studied the renal lesions of fifty-five patients with gout. In seventeen instances nephritis was observed, predominantly of the vascular type. Only four postmortem examinations were made, three showed vascular lesions and one showed glomerulonephritis. In thirty-eight of the fifty-five patients no evidence of nephritis or functional impairment of the kidneys was discovered. These authors find vascular disease and hypertension to be more frequent in gouty persons than in normal persons of corresponding age. The renal lesions which occur are believed in the majority of instances to be secondary to vascular change and not to occasional deposits of urates in the kidneys, which apparently do not seriously affect renal function.

26 Pappenheimer, A. M. The Effect of Experimental Reduction of Kidney Substance upon the Parathyroid Glands and Skeletal Tissue, *J. Exper. Med.* **64** 965 (Dec.) 1936.

27 Goldring, W., and Graef, I. Nephrosis with Uremia Following Transfusion with Incompatible Blood, *Arch. Int. Med.* **58** 825 (Nov.) 1936.

28 Schmitker, M. A., and Richter, A. B. Nephritis in Gout, *Am. J. M. Sc.* **192** 241 (Aug.) 1936.

Book Reviews

Therapeutic Agents of the Pyrrole and Pyridine Group By W F von Oettingen, M D, Ph D, Director of the Haskell Laboratory of Industrial Toxicology, Wilmington, Del Cloth Price, \$4.75 Pp 258, with 28 tables and 4 charts Ann Arbor, Mich Edwards Brothers, Inc, 1936

This book is the second in a series of monographs of the American Chemical Society. It is an important contribution to the pharmacologic literature. It consists of a systematic description, primarily pharmacologic but also chemical, of the substances the foundations of which are the pyrrole or pyridine nucleus that have been studied for their therapeutic activity. These two nuclei, which received their original interest and stimulus from coal tar chemistry, are the structural bases for many drugs. Among the accepted synthetic preparations may be mentioned isacfen, neo-iopa\, metycaine, diothane, eucaïne hydrochloride and homatropine. Among the accepted alkaloids of plant origin may be mentioned physostigmine, sparteine sulfate, atropine, scopolamine, cocaine and pelletierine tannate. They also form the bases for a large number of substances both synthetic and occurring naturally which are either important structural units of tissues, such as the amino-acid tryptophan, or substances which have been extensively studied pharmacologically in both animals and man. These last-mentioned compounds, although they have not been shown to be sufficiently worth while to become accepted medicinal substances, are nevertheless important, because from this vast amount of effort will come other chemical substances worthy of acceptance. It is interesting to note that the substances derived from these two nuclei have actions in almost all fields of pharmacology, including local anesthetics, antiseptics and anthelmintics, and are concerned with the vegetative nervous system, smooth muscle, the circulatory, respiratory and excretory systems and the central nervous system.

Although the book was written from the standpoint of chemical constitution and pharmacologic action, the author points out that this view does not solve all the difficulties. There are other factors, such as physicochemical properties, which when better understood will undoubtedly lead to more rapid progress in the synthesis of new and useful drugs.

This book is primarily for pharmacologists, libraries and those persons interested in the particular subject. The chemical data, other than those showing the structural formulas, are not extensive. The latter are, however, handled beautifully. The inclusion of many tables is another desirable feature.

The book represents a commendable attempt to publish a small edition of a technical subject inexpensively. The photolithograph process has been used, with inexpensive but satisfactory paper, neatly bound in serviceable cloth. The type is large, clear and legible. It is hoped that this experiment in the publishing of valuable scientific material will be successful.

The Practice of Medicine By Jonathan Campbell Meakins, M D, LL D Price \$10 Pp 1,343, with 505 illustrations, 35 in color St Louis C V Mosby Company, 1936

One must welcome this new addition to the ever increasing number of textbooks on the practice of medicine. Physically the work is a substantially bound volume of 1,310 pages, exclusive of the index. There are 505 figures, an unusually large number, 35 of them being in color. To quote the author "This is a pictorial age and many factual data are capable of graphic records. Therefore, I have diverted from the usual custom in text books on the practice of medicine and have inserted many illustrations with the hope that these may be more informative than a word description." The figures are aptly chosen to depict the important physical signs, microscopic and gross pathologic pictures, endocrine disturbances and roentgen findings fundamental to a complete and clear understanding of the problems

This is particularly true of the colored plates, which illustrate, for the most part, the types of cyanosis, oral lesions, cutaneous tests, eruptions, smears of bone marrow and peripheral vascular phenomena. However, some of the conditions illustrated are so rare that it hardly seems advisable for them to occupy so much of the limited space assigned to a textbook on medicine.

The book has a decided British flavor. Chapter 1 opens with a consideration of the approach to the patient. Here and throughout the text symptoms are stressed. They represent, says Meakins, the earliest manifestations of disease and are therefore of primary importance. "They are clues to the clinical riddles. For this reason they have been given particular prominence, and where possible their causation has been described and their significance has been pointed out." The remaining twenty chapters deal specifically with descriptions of the diseases themselves, starting with diseases of the nasopharynx and mouth and continuing through the various systems and organs to diseases of nutrition, metabolism, parenteral infections, allergic diseases and diseases due to abnormal environment, chemicals and drugs.

Only such a prodigious worker as Meakins, with the broad understanding and knowledge of disease that he possesses, could attempt and execute so well a textbook of these proportions. Except for the chapters on diseases of the nervous system, urinary tract, endocrine glands and metabolism, the book represents his authorship alone. As one might suspect from Meakins' interest in research, the sections on respiratory and circulatory diseases, particularly with regard to the significance and interpretation of symptoms, are exceptionally lucid. One may find in this book, as in any book, points which one feels are not adequately stressed. For example, the recent work in England and the United States on the virus theory of influenza is entirely ignored, and the virus theory is barely mentioned. Dengue, which is again making its appearance as a significant disease in the southern part of the United States, is not mentioned in the differential diagnosis of influenza. However, the greatest inadequacy in the entire text, in the opinion of the reviewer, is in the consideration of renal disease. Here the mechanisms of the fundamental expressions of renal insufficiency are barely considered, and the relationship of vascular nephritis to other types is not clearly defined.

One must welcome this book for a thoroughness and completeness not always attendant on a book of this type and for the simplicity of plan and expression which convey to the reader a clear picture of the diseases described.

Dietetics for the Clinician By Milton A. Bridges. Third edition. Price, \$10. Pp. 1,055, with 85 tables. Philadelphia: Lea & Febiger, 1937.

While diet is, of course, of immense importance in medicine, there are only a few diseases—above all diabetes—in which accurate dietary prescriptions are necessary. Indeed, it is better as a rule to lay down simple principles rather than to burden the patient with detailed lists. The reviewer's main feeling on seeing this immense volume was therefore one of curiosity as to how it was possible to fill over a thousand pages in dealing with the subject, but a casual glance at the contents reveals promptly a great deal that is of questionable value. It is true that all the major considerations of diet are well presented, but the book would be better without the introduction of meaningless diet lists by the hundred for every possible condition. Under the heading of scurvy, for example, one is given not only a list of the foods containing vitamin C but a list of the foods which contain little or no vitamin C. Two pages are taken up with sample menus for patients with scurvy which, beyond the presence of citrus fruit, are meaningless. When one comes to the section on gastro-intestinal disease, it is hard to restrain one's impatience. Why, for example, should spinach and a whole page of other harmless foods be "omitted" by persons with visceroptosis, even admitting that the condition requires special clinical consideration? It is news to the reviewer that apple sauce and bread should be "omitted" by patients with renal glycosuria and that cake, fish and fresh bread are bad for those with indicanuria. Detailed diets for patients with cholecystitis with hyperacidity and cholecystitis with mucous

colitis, indeed with any condition from enuresis to influenza, are given in this monumental compendium under the section quaintly headed "Diseases and Their Diets" The best part of the book is that containing elaborate reference tables on the composition of foods, in which the subject is covered from every standpoint

News and Comment

PAN AMERICAN MEDICAL ASSOCIATION

The *Queen of Bermuda* has been chartered for the Seventh Cruise-Congress of the Pan American Medical Association

The main part of the congress will be held in Havana Scientific sessions with operative clinics will be held on three days and will be divided into sections for the various specialties This year there are four new sections, on tuberculosis, gastro-enterology, dentistry and industrial medicine Meetings will be arranged with medical colleagues at the other ports of call

The Hotel Savoy-Plaza in New York and the National Hotel in Havana will be the official hotels

Applications for reservations should be addressed to the Pan American Medical Association, 745 Fifth Avenue, New York

AMERICAN COLLEGE OF PHYSICIANS

The Twenty-Second Annual Session of the American College of Physicians will be held in New York, with headquarters at the Waldorf-Astoria Hotel, April 4 to 8, 1938

The president, Dr James H Means, Boston, will have charge of the program of general scientific sessions Dr James Alexander Miller, New York, the general chairman of the session, will be in charge of the program of clinics and demonstrations in the hospitals and medical schools and of the program of round table discussions to be conducted at headquarters

PNEUMONIA DUE TO PNEUMOCOCCUS TYPE VII (COOPER) SPECIFIC SERUM TREATMENT

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AND

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NEW YORK

In our series *Pneumococcus* type VII (Cooper) was responsible for 65 per cent of the cases of pneumococcic pneumonia in adults and for 24 per cent of the cases of pneumococcic pneumonia in children

During the seven years from 1928 to 1935 there were observed in the wards of the Harlem Hospital 218 patients with pneumonia due to *Pneumococcus* type VII. Of these, 200 were adults and 18 were children. The number of cases and the relative incidence of this type of pneumonia varied from year to year. In the series for adults in the years 1929-1930 and 1930-1931 the cases of pneumonia due to *Pneumococcus* type VII were relatively most numerous, 37 cases (9 per cent). In the year 1934-1935 this type occurred in 24 cases, only 4.6 per cent of the total number of cases of pneumonia for that year.¹

Of the adult patients with type VII pneumonia, 157 (78.5 per cent) were men and 43 (21.5 per cent) were women. The predominance in men occurred in all decades except the eighth.

This study received financial support in part from the Metropolitan Life Insurance Company.

The cases reported here include those previously reported by one of us (J G M B) in connection with the use of therapeutic serum.

From the Littauer Pneumonia Research Fund of the New York University, College of Medicine, from the Medical Service, Harlem Hospital (Department of Hospitals), and from the Research Laboratories (Department of Health).

1 In the year 1935-1936 there were 85 cases (13.3 per cent) of type VII pneumonia.

MODE OF ONSET AND COURSE

In only 40 (20.6 per cent) of 194 adults was the onset preceded by a cold in the head or in the chest. In 152 cases (78.4 per cent) the illness started with a chill and in 175 cases (90.2 per cent) with pain in the chest (6 cases were omitted because the histories were unobtainable).

The graphs of the temperature of the 41 patients who were not given serum and who came to the hospital on the third day of the disease or earlier may be divided as follows. Twenty-three curves (56.1 per cent) showed a constantly elevated temperature of a single phase, 10 (24.4 per cent) were biphasic, that is, there was a drop in temperature of more than 3 F which lasted twenty-four hours or longer, and 8 (19.5 per cent) were polyphasic, having several such drops in temperature. The polyphasic temperature curves were typical of sepsis, displaying marked fluctuations of less than twenty-four hours' duration. Four patients did not show a rise in temperature above 102 F, yet 1 of these patients died. The 11 patients whose pulse rate was always below 110 survived.

SEVERITY

Type VII pneumonia is moderately severe. Twenty-eight (18.8 per cent) of the 149 adult patients who were not given serum died. The mortality was slightly higher among the men. Twenty-three (19.7 per cent) of the 117 men died, whereas only 5 (15.6 per cent) of the 32 women died.

The mortality among infants was highest. Two of 5 children under 2 years of age who did not receive serum died. All 10 children from 2 to 12 years of age and the 9 patients in the 12 to 20 year period survived. After the age of 50 the mortality was as high as among infants. Seventeen of the 104 men under 50 died, a mortality of 16.3 per cent, and 5 of the 12 men over 50 died, a mortality of 41.6 per cent. The death of one male was omitted from this series because his age was unknown. Three of the 29 women under 50 died, a mortality of 10.3 per cent, and 2 of the 3 women over 50 died, a mortality of 66.7 per cent.

The occurrence of high fever, rapid pulse rate or some menacing symptom, such as delirium, severe anoxia, distention, dehydration, pulmonary edema or a rating of less than 50 (in accordance with our method of rating given elsewhere²), characterized the cases of severe pneumonia. Cases of moderately severe pneumonia were those in which the rating was always between 50 and 70, and cases of mild pneumonia were those in which the rating never was below 75. In the series of adults, after excluding the 6 fatal cases in which there was an associated

² Bullowa, J. G. M. Use of Antipneumococcic Refined Serum in Lobar Pneumonia, J. A. M. A. 90:1349 (April 28) 1928.

lethal condition, pneumonia was severe in 73 (37.6 per cent) of the 194 cases, moderate in 86 (44.3 per cent) and mild in 35 (18 per cent)

Death occurred in 47.4 per cent of those who were irritable, 48.3 per cent of those who were delirious, 85.7 per cent of those who had pulmonary edema and 47.6 per cent of those who were dehydrated. The 2 patients who hiccupped died. The influence of these and additional factors are shown in table 1.

TABLE 1—*Occurrence of Symptoms and Effect on Outcome Among Two Hundred Adult Patients with Type VII Pneumonia**

	All Cases in Which There Were Symptoms	Percentage of Total (200) Cases	Fatal Cases in Which There Were Symptoms	Percentage of Fatal Cases (33) in Which Symptoms Occurred	Fatality in Cases in Which Symptoms Occurred, Percentage
Onset					
Preceded by cold in head or chest	40	20.6	5	16.1	12.5
Chill at onset	152	78.4	23	74.2	15.1
Pain in chest	175	90.2	26	83.9	14.9
Course					
Temperature always below 102 F	4	2.0	1	3.0	25.0
Pulse rate always below 110	11	5.5	0	0.0	0.0
Symptoms					
Cyanosis	109	54.5	22	66.7	20.2
Anoxemia (requiring oxygen)	88	44.0	22	66.7	25.0
Headache	121	60.5	19	57.6	15.7
Apathy	45	22.5	12	36.4	26.7
Irritability	19	9.5	9	27.3	47.4
Sleeplessness	68	34.0	10	30.3	14.7
Delirium	29	14.5	14	42.4	48.3
Sedatives required	139	69.5	21	63.6	15.1
Vomiting	59	29.5	13	39.4	22.0
Diarrhea	5	2.5	1	3.0	20.0
Distention	75	37.5	14	42.4	18.7
Icterus	8	4.0	2	6.1	25.0
Pulmonary edema	14	7.0	12	36.4	85.7
Dehydration	21	10.5	10	30.3	47.6
Epistaxis	11	5.5	0	0.0	0.0
Hemoptysis	10	5.0	2	6.1	20.0
Herpes	13	6.5	0	0.0	0.0
Hiccup	2	1.0	2	6.1	100.0
Pleurisy	139	69.5	24	72.7	17.3
Kahn reaction† (3+ or 4+)	23	32.4	0	0.0	0.0

* Of the 200 patients, 167 recovered and 33 died. In 6 cases the history was not obtainable.

† For only 71 of the 200 patients was the Kahn reaction studied. Of these 71 patients, 66 recovered and 5 died.

BACTEREMIA

Nonserum Treatment—Eighteen of the 149 patients who did not receive serum treatment had bacteremia, an incidence of 12.1 per cent. Thirteen of these 18 patients died, a mortality of 72.2 per cent.

In 3 instances the time of onset of bacteremia was known because of previously sterile cultures. The blood of one patient became invaded on the eighth day of illness. The heart blood of another patient contained bacteria when taken on the seventh day post mortem, and that of another patient, when taken on the ninth day post mortem. The cultures of the blood of the other patients gave positive results for type VII pneumococci when the patients were admitted to the hospital.

TABLE 2—Data for Patients with

Sex	Age	Year	Outcome	Day of Disease																	
				1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
				No Serum Treatment (Mortality, 72.2 per Cent)																	
F	35	1929	R			Br				—		T									
M	36	1936	R			Br	37 38	8 0	150 12	Br	—	—	—		T						
M	42	1932	R			Br		7 8	5 4	3 0	—	—									
M	42	1933	R				5 8		5 4	8 7	Br	Br	Br	—	Br T	—				—	
F	23	1933	R				—		—		Br	—	—	—	—		—	—	—	Br	
M	56	1928	D						2 3		Br	Br	D								
M	45	1929	D												—				Br	D	
M	37	1929	D					488 424	D												
M	48	1929	D							Br	Br				Br D						
M	38	1930	D			1 0				2 0	D										
M	42	1930	D													Br	Br	2 0	—		
F	29	1930	D			∞	∞ D														
M	23	1930	D			—	—	—				— Pm Br D									
M	29	1930	D			7 16			51 18	∞	Pm Br D										
M	40	1930	D						3 2		2 0	5 9	D								
F	26	1933	D						2 3	—	—	—	Br	Br	110 82	368 240	344 288	D			
M	50	1933	D																		
M	47	1934	D			—	—			Pm 11 25 D											
				Serum Treatment (Mortality, 40 per Cent)																	
M	33	1931	R				3 6	18 20 S	2 2 S	— S	— S	— T S									
M	55	1933	R				3 0		36 32 S	— S	— S			T							
M	30	1934	R					Br	— S	— T S											
M	47	1934	D				280 230	Br Br S	40 45 S	50 55	Br S	Br S	1,090 S	Pm Br D							
F	19	1934	D				—		— S		Pm Br S D										

* R indicates recovered, D, died, —, sterile culture, Pm, postmortem examination of heart blood, numbers, colony counts, ∞, innumerable colonies, Br, positive result of broth culture, T, termination of elevated temperature, S, serum treatment.

*Type VII Pneumonia with Bacteremia**

19	20	21	22	23	24	26	30	33	35	52	?	Comments
No Serum Treatment (Mortality, 72.2 per Cent)												
												Empyema, pus from chest contained type VII pneumococcus
												T Pus from chest contained type VII pneumococcus, indeterminate with empyema
	—		—		T							Bed sore
												Purulent arthritis and pericarditis, culture of material from knee showed type VII pneumococcus
												One colony was fished and was not found to contain type VII pneumococcus until sixth day
Br	Br	—				—	—	—	—		D	Empyema, pericarditis and erysipelas
												Obesity
												Delirium tremens
												10 Died on day after admission to hospital in alcoholic coma
												11 Alcoholic addict
Serum Treatment (Mortality, 40 per Cent)												
												Alcoholic addict serum 20,800 units on 5th, 59,200 on 6th, 236,000 on 7th, 400,000 on 8th and 80,000 on 9th day
												Empyema, pus from chest contained type VII pneumococcus Serum 25,000 units on 6th, 325,000 on 7th and 87,500 on 8th day
												Serum 200,000 units on 6th and 60,000 on 7th day
												Icterus serum 130,000 units on 4th, 208,000 on 5th, 135,000 on 7th, 265,000 on 8th and 348,000 on 9th day
												Septic abortion, serum 86,000 units on 6th and 80,000 on 7th day

Of the 13 whose blood had less than 50 colonies per cubic centimeter or showed positive results of culture only in broth, 9 died and 4 survived and of 5 whose blood contained more than 50 colonies per cubic centimeter in one or both plates, 4 died and 1 survived. The following complications developed in the cases of bacteremia. One of the patients whose blood showed 50 colonies or more per cubic centimeter had empyema and recovered. One of the patients whose blood showed a count of less than 50 colonies per cubic centimeter died of purulent pericarditis and arthritis. Another patient had empyema, pericarditis and erysipelas, resulting in death. Another had empyema and recovered.

Serum Treatment—Among the 5 patients who received serum treatment, 1 received it on the fourth day of illness and the others later. One patient whose colony count was under 50 per cubic centimeter, had empyema and recovered. There were 2 deaths, 1 of which was complicated by septic abortion. Broth culture gave positive results post mortem. The other patient was treated on the fourth day, when the broth culture alone gave positive results, although there had been 280 colonies per cubic centimeter the previous day, this patient had severe icterus. In none of these 5 patients treated with serum did bacteremia develop after serum treatment was begun, except in a patient for whom the only positive result of blood culture was obtained post mortem. This is the patient previously mentioned whose condition was complicated by septic abortion. In table 2 are shown the day of the disease on which a positive result of blood culture was obtained and the number of and changes in the colony counts.

COMPLICATIONS AND ASSOCIATED DISEASES

Nonserum Treatment—The complications and associated diseases were as follows. There were 6 recognized cases of empyema, and 3 of the patients recovered. Two cases of encapsulated empyema were discovered post mortem. One patient with empyema associated with pericarditis and erysipelas died. Another patient with pericarditis and purulent arthritis died. One patient with purulent arthritis and myositis died. One patient died of meningitis. One patient recovered from a postpneumonia psychosis. Bed sores developed on 4 patients, 2 of whom died, one of the patients who died also having parotitis, and the other, fibroid tumors. Three of the markedly obese patients died. Three patients had diabetes mellitus, and all recovered. One patient had fibrillation during the disease and recovered. Of 8 patients with a history of alcoholic indulgence, 3 died, 2 others entered the hospital with delirium tremens and died, 1 patient with syphilitic heart disease recovered. Three patients had rheumatic heart disease. One patient had carditis and pericarditis, and 1 had mitral insufficiency, both

recovered One obese patient, previously mentioned, had aortic regurgitation with fibrillation and died One patient had an intestinal obstruction and died

Albuminuria occurred in 101 patients, 50.5 per cent of those whose urine was examined Twenty-three of these patients died The grade of albuminuria apparently had no influence on the outcome In 18 patients there was a trace of albuminuria, 7 (38.9 per cent) died Forty-one patients showed a 1+ reaction of the urine for albumin, 8 (19.5 per cent) died Forty-two showed a 2+, a 3+ or a 4+ reaction for albumin, 8 (19 per cent) died

One patient who had been pregnant for seven months recovered, but 1 patient who had pneumonia post partum died One patient had phlebitis and recovered One patient died suddenly, with great dyspnea One patient who had had a septic abortion died A patient who had a pulmonary abscess died

Serum Treatment—Fifty-one patients with type VII pneumonia were treated with serum Three of these patients were excluded from the series because of serious accompanying conditions The first patient had rheumatic carditis and pericarditis with effusion with type VII nonbacteremic pneumonia, and recovered The second of these 3 patients had a septic abortion during type VII pneumonia, with bacteremia, and died The third patient had type VII pneumonia without bacteremia but with aortic regurgitation and chronic myocarditis and died

Three patients who died were also excluded from the group of 149 patients who were not given serum treatment One patient had erysipelas with empyema and type VII pneumonia with bacteremia The second had intestinal obstruction without bacteremia and the third had a postpartum infection without bacteremia

The death rate for patients treated without serum, 17.1 per cent ± 3.1 , may be compared with that for those treated with serum, 6.2 per cent ± 3.4 The ratio of the difference to the standard error is 2.35, or, expressed in another way, there are 981 chances in a thousand that the difference in the death rates is significant Twelve of the 17 patients who were bacteremic and did not receive serum died, a mortality of 70.6 per cent, as opposed to 1 death among 4 patients treated with serum, a mortality of 25 per cent The ratio of significance is 1.88, or 940 chances in a thousand Thirteen (10.1 per cent) of the 129 patients who did not receive serum and who did not have bacteremia died, and 2 of the 44 who received serum treatment died, a mortality of 4.5 per cent The ratio of significance is 1.38, or 831 chances in a thousand (chart 1)

The 2 patients without bacteremia who received serum and who died were an obese patient who had large fibroid tumors, a bed sore and otitis media and a patient in whom cyanosis and marked dyspnea suddenly developed

As shown previously type VII pneumonia is moderately severe. Twenty-four of the 55 patients who had severe pneumonia and did not receive serum died, a mortality of 43.6 per cent, and 3 of the 18 who

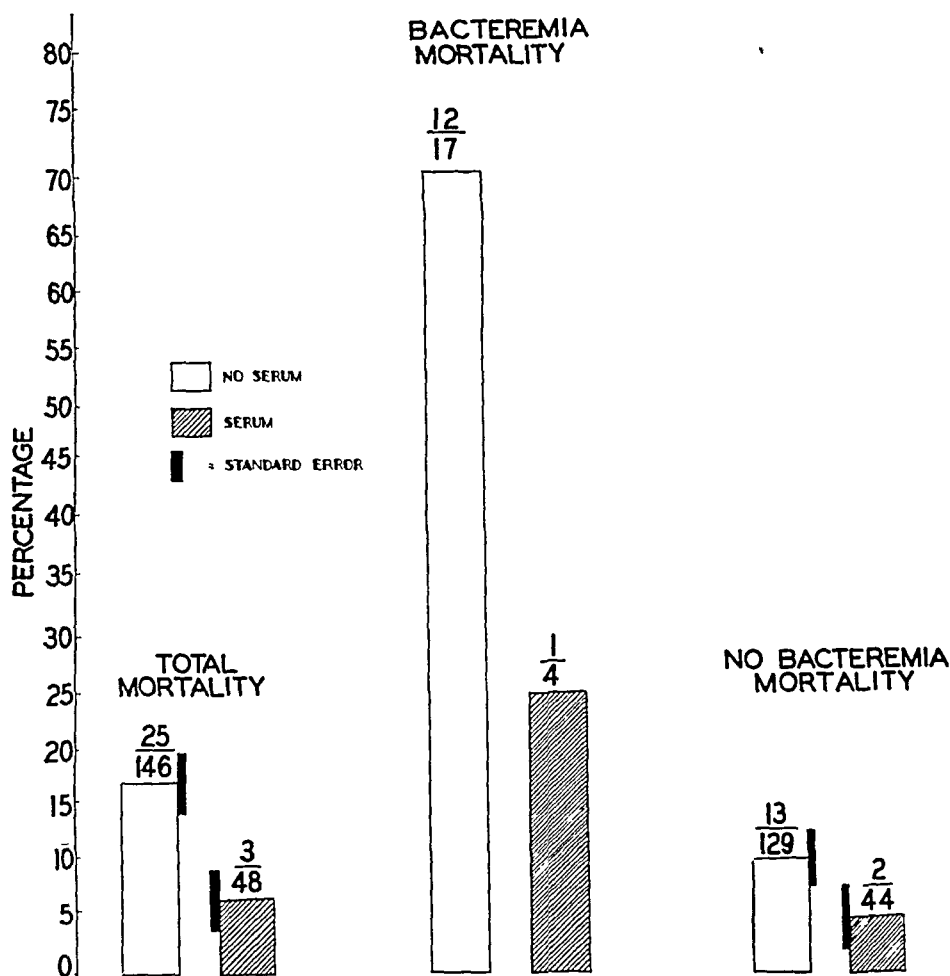


Chart 1—Type VII pneumonia, showing the effect of serum treatment on the mortality, 1928 to 1935. The ratio of significance for the total mortality is 2.35, or $\frac{981}{1000}$. The ratio in the cases in which there was no bacteremia is 1.38, or $\frac{831}{1000}$.

had severe pneumonia and received serum died, a mortality of 16.7 per cent (chart 2)

In chart 3 are shown the days after onset that the disease terminated after the commencement of serum treatment (black circles) and the days after onset of termination of disease for patients who did not

receive serum (white circles) The accumulation of the black dots to the left shows the shortening of the illness in the cases in which serum was given The flags on dots or circles indicate patients with bacteremia

Combining the cases in which the disease terminated on the same day and on the first day after the patient's admission to the hospital or the commencement of serum treatment, it is found that in 55.6 per cent of the cases in which serum was given and in only 22.7 per cent of the cases in which no serum was given did the disease terminate then By the conclusion of the second day after the commencement of serum treatment in 33 (73.3 per cent) cases had the illness terminated, whereas

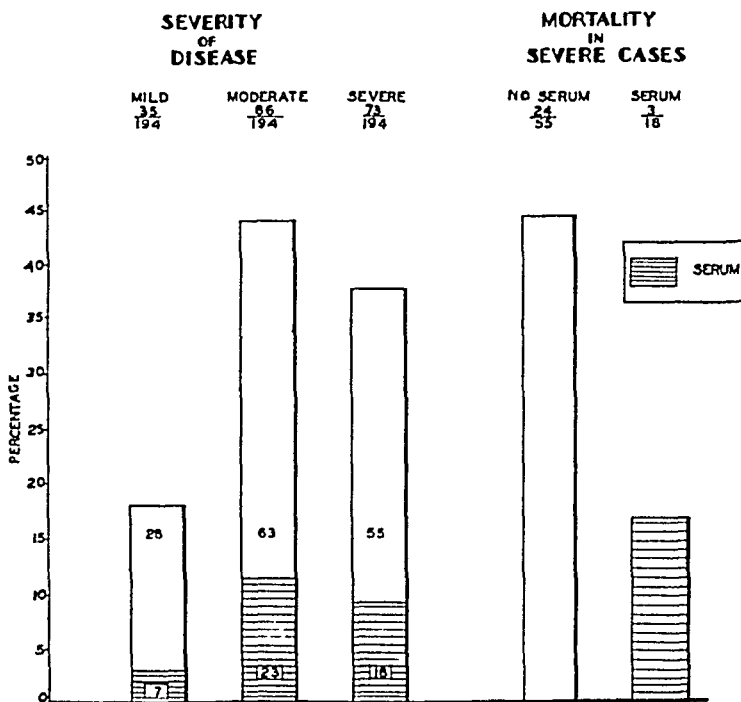


Chart 2—Summary of data for 194 patients with type VII pneumonia, July 1, 1928, to July 1, 1935 (in 48 cases serum was given, and in 146 cases no serum was given) The data for 6 patients were omitted because of accompanying lethal disease (table 3)

in 45 (only 37.8 per cent) cases in which serum was not given the illness terminated on the second day

RELATION OF SERUM TREATMENT TO COMPLICATIONS

The group of 14 patients who received serum treatment before the fifth day of the disease had no complications Five of the 36 patients treated on the fifth day or later had complications, an incidence of 13.9 per cent One of these died, a mortality of 20 per cent One patient without complications was omitted because the day of onset of disease was not known Eighteen of the 149 patients who did not receive serum

TABLE 3—Data for Six Patients with Accompanying Lethal Disease

Case	Complicating Conditions	Treat ment	Invasion of Blood	Severity	Outcome
1	Rheumatic carditis and pericarditis	Serum	No bacteremia	Severe	Recovered
2	Septic abortion	Serum	Bacteremia	Severe	Died
3	Aortic regurgitation and chronic myocarditis with fibrillation	Serum	No bacteremia	Severe	Died
4	Erysipelas and empyema	No serum	Bacteremia	Severe	Died
5	Intestinal obstruction	No serum	No bacteremia	Moderate	Died
6	Postpartum complications	No serum	No bacteremia	Severe	Died

TABLE 4—Type VII Pneumonia and Additional Infections, 1928 to 1935

Sex	Age	Year	Source of Type VII Pneumococcus	Simultaneous Infections	Successive Infections with	Outcome	
						Serum Treatment	No Serum Treatment
M	34	1929 1930	Lung (suction)	Hemolytic streptococcus (obtained post mortem from heart blood), type III pneumococcus (chains) in sputum			Died
M*	38	1929 1930	Blood culture	Type II pneumococcus (sputum)			Died, received serum for type II pneumonia
M	31	1930 1931	Mouse heart		Bact pestis caviae Blood culture		Died
M	32	1930 1931	Blood culture		Hemolytic streptococcus Blood culture		Died
M	32	1931-1932	Lung (suction)		Staph aureus Blood culture		Died
M*	17	1931 1932	Lung (suction)	Type I pneumococcus (sputum)			Recovered, received serum for type I pneumonia
M*	55	1932 1933	Pus from chest Blood culture	Type I pneumococcus (mouse heart)		Recovered	
M	50	1932 1933	Blood culture		Hemolytic streptococcus Heart blood, pericardial fluid, spinal fluid, lung (suction) post mortem	Died	
F	29	1932-1933	Lung (suction)		Hemolytic streptococcus Heart blood, pericardial fluid, lung (suction) post mortem	Died	
M	37	1933 1934	Sputum	Type XIII pneumococcus (sputum)			Recovered
M	49	1934 1935	Pus from chest Blood culture		B coll Prostatic abscess and blood culture	Died	
F	24	1934 1935	Lung (suction)		B sulpestifer Blood culture	Recovered	

* These cases are included in the series of 200 adults. The others were omitted because the primary infection was indefinite.

ADDITIONAL INFECTIONS

In table 4 are shown the data for 12 patients with type VII pneumonia associated with another organism, 8 of these died and 4 recovered. The source of the pneumococcus in 5 cases was the blood culture and in 5 cases material obtained by pulmonary suction, in 1 case the organism was obtained from the heart blood of a mouse after inoculation with sputum, and in 1 directly from the sputum. In 5 cases the second organism was present at the same time as the pneumococcus, and in 7 cases its appearance succeeded the primary type VII pneumonia.

The complicating organism was *Streptococcus haemolyticus* in 4 cases, *Staphylococcus aureus* in 1 case, *Bacterium pestis caviae* in 1 case, *Bacillus supestifer* in 1 case, *Bacillus coli* in a prostatic abscess in 1 case, *Pneumococcus* type I in 1 case, *Pneumococcus* type II in 1 case and *Pneumococcus* type XIII in 1 case.

Seven patients did not receive serum for type VII pneumonia. One with type I pneumococcus as coinvasader received serum for type I but not for type VII pneumonia and recovered. One in whom type II pneumococcus was found in the sputum and type VII in the blood culture received serum for type II but not for type VII pneumonia and died. Five received serum for type VII pneumonia and 2 of them recovered.

When the hemolytic streptococcus was present subsequent to or simultaneously with invasion by the type VII pneumococcus the outcome was uniformly fatal.

CHILDREN

During the seven years 18 cases of type VII pneumonia were observed among children. Of these, 6 were under 2 and 12 were from 2 to 12 years of age. Of the infants under 2 years, 1 who was 8 months old and had meningitis due to type VII pneumococcus died, and another of 3 months with pericardial effusion due to type VII pneumococcus with bacteremia died, neither of the infants received serum. A 10 month, a 19 month and a 20 month old infant recovered without serum. An 11 month old infant received serum on the eleventh day of illness, had empyema and recovered.

All the children over 2 years of age survived, whether they received serum or not. One of the children who was given serum on the tenth day had type VII empyema and recovered.

None of the children received serum sufficiently early to determine whether complications would have been prevented by early serum treatment. The cases are too few to permit the drawing of conclusions as to the value of serum in the treatment of type VII pneumonia in children (table 5).

TABLE 5—*Type VII Pneumonia in Children, 1928 to 1935*

Sex	Age	Year	Day of Termination of Fever	Blood Culture	Pulmonary Involvement	Comments	Outcome
No Serum Treatment (15 Cases)							
M	8 mo	1929 1930	10th (died)	None	Upper and middle lobes of right lung	Meningitis, type VII pneumococcus	Died
F	5½ yr	1929 1930	9th	None	Pleurisy, lower lobe of right lung		Recovered
M	6 yr	1929 1930	8th	None	Lower lobe of right lung		Recovered
M	20 mo	1930 1931	7th	Sterile	Upper lobe of right lung	Meningism	Recovered
M	5 yr	1930 1931	5th	Sterile	Pleurisy, lower lobe of left lung		Recovered
M	6 yr	1930 1931	9th	Sterile	Lower lobe of left lung		Recovered
M	11 yr	1930- 1931	7th	Sterile	Pleurisy, lower lobe of left lung	Lung suction, type VII pneu- mococcus	Recovered
M	9 yr	1931 1932	7th	Sterile	Lower lobe of left lung	Lung suction, type VII pneu- mococcus, delirium	Recovered
F	19 mo	1931 1932	9th	None	Upper and lower lobes of left lung		Recovered
M	5 yr	1931 1932	6th	Sterile	Upper lobe of right lung	Lung suction, type VII pneu- mococcus, purulent otitis media	Recovered
M	3 mo	1932 1933	17th (died)	Heart blood post mor- tem contained type VII pneu- mococcus	Pleurisy, upper lobe of right lung	Postmortem pericardial fluid, type VII pneu- mococcus	Died
M	4 yr	1932 1933	3d	Sterile	Lower lobe of right lung		Recovered
M	10 mo	1933- 1934	Onset indefi- nite	None	Bronchopneumonia	Rickets	Recovered
M	10 yr	1933 1934	7th	None	Lower lobe of left lung	Lung suction type VII pneu- mococcus	Recovered
F	7 yr	1933 1934	5th	Sterile	Pleurisy, upper lobe of left lung		Recovered
Serum Treatment (3 Cases)							
F	11 mo	1930 1931	?	Sterile	Pleurisy, upper lobe of left lung	Empyema, type VII pneumococcus, transfusion, lung suction, type VII pneumococcus rickets, serum given on 11th day	Recovered
M	5 yr	1930 1931	7th	Sterile	Pleurisy, lower lobe of right lung	Lung suction, type VII pneu- mococcus serum given on 6th day	Recovered
M	7 yr	1931 1932	14th	Sterile	Pleurisy, lower lobe of right lung	Empyema, type VII pneumococcus, meningism serum given on 10th day	Recovered

• CONCLUSION

It appears as the result of these studies that among the patients who received serum the mortality was significantly reduced, as shown in chart 1, and that the duration of illness was shortened, even when serum treatment was begun on the fifth, sixth or seventh day of illness (chart 3)

The patients to whom serum was administered before the fifth day of illness had no complications. For the group of patients who received serum on the fifth day or later and for the group who were not given serum the incidence of complications was approximately the same, but the mortality among those with complications who were treated on the fifth day or later was lower than the mortality among the corresponding group of patients who did not receive serum treatment

FUNCTIONAL ACTIVITY OF RENAL EPITHELIUM IN CERTAIN TYPES OF NEPHRITIS

AS INDICATED BY SECRETION OF AMMONIA

A P BRIGGS, M D

AUGUSTA, GA

Since ammonia appears to be elaborated by the renal tubules, the activity of its production might, if looked at from a proper theoretical point of view, throw light on the functional state of the tubular division of the renal parenchyma, an altered functional state with nephritis might be reflected in a corresponding alteration of the activity of production of ammonia

The suggestion for the present study came with the development of a new view concerning the mechanism which results in the production of ammonia by the kidney¹ According to this view, the production of ammonia by the renal tubules is stimulated by and serves to neutralize the acid residue which remains to flow through the tubules after resorption of the alkaline threshold moiety from the glomerular filtrate² In contrast to this theory is the classic concept, which assumes that production of ammonia responds to the requirements of the body for the excretion of acids, which could not otherwise be excreted in the urine without drawing from the body an excessive amount of the essential alkaline elements It further assumes that the production of ammonia is diminished when it is desirable for the body to become rid of excess fixed base

Some of my reasons for dropping this view were as follows 1 The production of ammonia is not necessarily increased when there is a surplus of acid in the body to be excreted Such an exception occurs after administration of potassium chloride, when because of the rapidity of the excretion of potassium into the urine a surplus of chloride remains And this surplus is perfectly analogous to that which remains

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1 Briggs, A P (a) The Acidosis of Nephritis Its Clinical Significance, Arch Int Med **49** 56 (Jan) 1932, (b) Excretion of Ammonia and Neutrality Regulation, J Biol Chem **104** 231 (Feb) 1934

2 This view has been worded to fit the current filtration-resorption theory of urinary secretion If it should be found that waste acid is secreted by the tubules, it would still appear that stimulation of the production of ammonia results from irritation of acid

after administration of calcium chloride because of excretion of calcium by the intestine. According to the classic base-regulatory theory, production of ammonia should be increased after administration of either potassium chloride or calcium chloride. This is not true. According to the stimulus-response theory, an increase should be observed only after the administration of calcium chloride, and this is true. 2 The production of ammonia is not necessarily decreased when the body is loaded with a surplus of fixed base. Such an exception has been observed to follow the administration of dibasic sodium phosphate, when increased production of ammonia was associated with more rapid secretion of phosphate than of sodium. Production of ammonia in this instance is again understandable from the stimulus-response point of view and not from the base-regulatory concept. 3 Diuresis from water, urea or other neutral substances does not increase the formation of ammonia, even though the bicarbonate content of the plasma is seriously depleted. This is a flat contradiction to the base-regulatory theory, but it is in harmony with the view taken here, for the diuresis prevents the formation of an acid residue within the tubules.

All of these special circumstances, as well as all other experimental maneuvers, show fluctuations of excess acid in the urine to be accompanied with a similar fluctuation of the amount of ammonia.

It should be pointed out, in addition to what has already been said, that the classic concept of the production of ammonia is not at all compatible with the current filtration-resorption view of urinary secretion. For the various acids of the urine are thought to be filtered into the tubule passively by the glomerulus, the production of ammonia can hardly have anything to do with filtration of acid. Conceivably, resorption of fixed base might be facilitated by secretion of ammonia, but far too much base is resorbed to be accounted for by the ammonia produced, even with a highly acid ash diet. Moreover, with a change to an alkaline ash diet, the quantity of base resorbed is thought to remain unchanged, while the secretion of ammonia falls off to a minimum.³

It is proposed here to show further examples of the parallelism between the amount of ammonia formed by the kidney and the amount of excess acid excreted. Then, with an established normal relationship for comparison, a number of observations will be reported showing the response, in production of ammonia to excess acid, with certain types of nephritis.

³ Peters, J. P. *Body Water*, Springfield, Ill., Charles C. Thomas, Publisher, 1935. Peters has criticized my views and has stated the conclusion that they should be rejected. Actually he has failed to point out any instance in which a change in excess of acid over fixed base in the urine is not accompanied with a similar change in secretion of ammonia. His discussion of the inconsistencies of the accepted view seemed incomplete and far from convincing.

EXPERIMENTAL METHOD

The normal subjects of this study were persons associated with the laboratory or patients showing no evidence of renal disease. The two groups of nephritic patients studied were (1) those giving clinical and laboratory evidence of an advanced stage of arteriosclerotic or hemorrhagic nephritis (these are referred to as patients with contracted kidneys) and (2) patients with the nephrotic syndrome.

Specimens of urine were collected over various periods during the day or night. Usually before a daytime study was made an acid or acid residue salt was taken by mouth, as indicated in the tables. The importance of preventing an alkaline tide during the period of study is obvious, for the excess of base excreted during this phase might approximately balance the excess of acid excreted during the remaining part of the period and the ammonia excreted during the latter phase would appear out of all proportion to a slight excess of acid for the total period. A continuous secretion of excess acid was assumed for the night periods.

In the collection of urine from women, either the vulva was first swabbed with physiologic solution of sodium chloride or the specimen was obtained by catheter.

Chloroform and thymol were used as preservatives.

Chemical Methods—Chloride was determined by a modified Volhard-Harvey titration and sulfate by the method of Fiske. For phosphate the uranium titration was employed. Phosphate was calculated as monovalent, for the reason that administration of a large quantity of phosphoric acid^{1a} stimulates the production of sufficient ammonia to reduce the acidity of the urine to approximately p_H 5, i. e., the vicinity of the point at which 1 hydrogen ion is completely neutralized.

For the same reason it was assumed that organic acid weaker than monobasic phosphate would have relatively little excitation for the production of ammonia, the strong organic acid reported is that fraction which titrated between the acidities of fifteenth-molar potassium phosphate and hundredth-molar citric acid. Since the purpose was to develop a technic which would be applicable to albuminous urine, such as is obtained from nephritic patients, it was desirable to remove albumin more completely than by acidification and heat. A little study indicated that a preliminary precipitation with zinc hydroxide removes albumin completely and serves also to remove phosphate, as is ordinarily done by calcium hydroxide. A little lactic acid is removed by this precipitation, and appreciable quantities of tartaric and citric acid may be removed, however, a comparison was made with the usual calcium hydroxide filtrate for normal urine, and similar values for strong organic acid were obtained. The zinc filtrate was found to be practically free from pigment, so that good color matches were obtained with the indicators employed. Skatole, if present, does pass into the zinc filtrate and interferes by producing a reddish coloration. In order to determine the correction for creatinine, a solution of creatinine and zinc chloride was precipitated and titrated as will be outlined presently. It was found that about 43 per cent of the creatinine was titrated over the range taken for strong organic acid.

The procedure employed was as follows. From 10 to 30 cc of urine was diluted with water and 10 cc of half-normal sodium hydroxide to a volume of 40 cc, precipitated with 10 cc of a 10 per cent solution of zinc sulfate and filtered. One 15 cc aliquot of the phosphate-free and protein-free filtrate was titrated with tenth-normal hydrochloric acid, methyl red being used as indicator, to match a standard containing the same amount of indicator in a similar tube and diluted with fifteenth-molar potassium phosphate. Comparisons were made

by looking down through the tubes at a white plate. Another 15 cc aliquot was similarly titrated to match a standard of hundredth-molar citric acid, bromphenol blue being used as indicator.

The difference between the two titrations was taken as the basis for the calculation. A correction was made for the blank titration on the reagents.

Fixed base was determined by a technic essentially similar to that of Stadie and Ross (phosphate was removed with ferric sulfate at p_H 5). For ammonia the aeration technic of Cullen and Van Slyke was employed and for creatinine the usual Folin and Wu method.

In calculating the excess acid, no consideration was given to the influence of creatinine as an organic base. The omission of this organic base tends to balance the omission of weak organic acid.

It became obvious early in the study that the ammonia ratio was influenced by the rate of flow of urine. The rate has therefore been calculated and is expressed in cubic centimeters per kilogram per hour. This expression was chosen for the reason that kidney weight, body weight and urine volume increase together during growth.

The ammonia ratio was calculated as

$$\frac{NH_3}{(Cl + H_2 PO_4 + SO_4 + \text{strong organic acid}) - (\text{fixed base})}$$

All the values were expressed as milliequivalents.

RESULTS

Inspection of the results for normal subjects in table 1 reveals that there is no good correlation between the quantity of excess acid and the ammonia ratio. It may be noticed also that the ammonia ratio is low when the rate of flow is fast and high when the rate is slow.

The relation between the rate of flow and the ammonia ratio is shown better in the accompanying chart. Here it becomes apparent that there is a definite relation between excess acid, the production of ammonia and the rate of flow of urine. That the ratio is so influenced by a local factor, the rate of flow, is entirely meaningless from the base-regulatory point of view, it is, however, what might be expected from the stimulus-response point of view. For with a more rapid rate, acid flowing through the tubules makes less intimate contact with epithelium.

At the slower rates the excess of strong acid is about 100 per cent neutralized. This finding, at slow rates, of a quantity of ammonia approximately equal to the excess of strong acid is evidence that the factors creatinine and weak organic acid, omitted in the calculation, are not significant or tend to balance.

Ratios obtained after the administration of large quantities of ammonium salts are not noticeably high, they fall in with the rest of the values for normal subjects given in the chart. This result might be anticipated, for most of the ammonia is converted to urea, and a slight increase of ammonia in the plasma and glomerular filtrate should result in only a corresponding decrease in the supplementary ammonia.

TABLE 1—*Urinary Acids and Bases and Ammonia Ratios at Various Rates of Flow*

Test Subject	Chlorine	Sulfate	Phosphate	Strong Or Organic Acid	Fixed Base	Excess Acid	Ammonia	Ratio, %	Rate of Flow†	Comments
1 A P B	19 15	6 50	5 77	4 13	25 63	9 92	9 75	98	0 40	Night urine
2 A P B	23 30	5 33	5 17	7 40	30 20	11 00	11 32	103	0 38	Night urine
3 A P B	15 70	4 23	3 92	6 75	20 90	9 70	7 13	74	0 70	Night urine
4 A P B	21 92	1 35	4 26	11 58	29 30	9 81	9 02	92	0 61	Night urine
5 A P B	20 06	1 75	0 66	2 83	20 02	5 28	3 81	72	1 67	30 cc of normal hydrochloric acid
6 A P B	5 64	0 43	0 42	2 04	7 18	1 35	0 84	62	2 00	20 cc of normal hydrochloric acid
7 A P B	5 63	0 30	0 42	2 52	7 11	1 76	1 06	60	2 24	25 cc of normal hydrochloric acid
8 A P B	27 18	2 11	0 53	1 96	29 80	1 98	1 50	76	0 93	25 cc of normal hydrochloric acid
9 A P B	9 35	1 49	1 78	1 22	10 92	2 92	2 48	85	0 98	60 cc of tenth molar phosphoric acid
10 A P B	9 63	0 74	1 53	1 43	11 35	1 98	1 59	80	1 46	60 cc of tenth molar phosphoric acid
11 A P B	13 16	0 73	2 09	2 61	15 70	2 89	2 24	78	1 37	60 cc of tenth molar phosphoric acid
12 A P B	27 17	3 72	0 75	2 17	24 51	9 30	5 03	54	1 67	20 cc of 5% ammonium sulfate
13 A P B	20 10	7 17	5 28	5 23	26 56	11 22	9 49	84	0 39	Night urine
14 A P B	17 30	1 15	1 20	2 38	20 40	1 63	1 40	86	0 58	20 cc of normal hydrochloric acid
15 A P B	22 31	4 08	1 84	1 52	22 40	7 35	6 98	95	0 35	Night urine
16 A P B	22 88	1 43	1 40	3 55	26 12	3 14	2 13	68	0 67	5 Gm of ammonium chloride
17 A P B	29 00	2 74	0 60	0 97	30 64	2 67	2 35	88	0 70	4 Gm of ammonium chloride
18 A P B	14 25	2 61	0 93	2 63	16 25	4 17	3 46	83	1 00	3 Gm of ammonium sulfate
19 A P B	19 50	4 43	3 54	3 41	25 50	5 38	5 66	105	0 36	Night urine
20 A P B	30 90	2 20	1 10	1 55	30 21	5 54	4 97	90	0 90	5 Gm of ammonium chloride
21 A P B	20 08	0 90	0 38	1 48	18 60	1 24	3 03	72	1 90	7 Gm of ammonium chloride
22 E	20 55	1 44	1 38	1 48	20 50	4 35	4 05	93	0 73	Exophthalmic goiter
23 E	17 02	4 09	1 57	3 81	21 90	4 59	3 63	79	0 84	Exophthalmic goiter
24 J W	17 55	3 48	3 08	4 05	20 05	8 11	7 37	91	0 40	Arthritis
25 G O B	15 20	4 08	3 51	1 45	21 00	3 24	3 52	108	0 28	Night urine
26 J A	16 80	3 50	2 52	2 73	23 70	1 91	1 75	92	0 51	Aged 12 years
27 I S	14 70	4 39	3 12	1 86	18 58	5 79	4 62	80	1 34	Aged 7 years
28 I S	15 83	3 68	3 25	2 17	20 22	4 71	3 43	73	1 48	
29 M S	13 51	4 22	7 74	2 40	14 76	13 11	8 48	65	1 38	Aged 3 years
30 M S	21 33	3 77	4 18	2 58	18 10	13 76	8 48	62	1 52	
31 G B Jr	17 50	2 59	2 22	2 29	21 95	2 65	2 11	80	1 08	Aged 7 years

* The results in tables 1 to 3 are expressed as milliequivalents per hundred cubic centimeters of urine

† The rate of flow of urine is given in cubic centimeters per kilogram per hour

produced for neutralization. The administration of ammonium chloride provides a convenient way of establishing a large excess of strong acid which can be accurately determined.

Tubular Function in Nephritis with Contracted Kidneys—Ratios obtained for patients with this type of nephritis are shown in table 2. On the chart they are observed to fall to the left of the normal zone, the zone of low response.

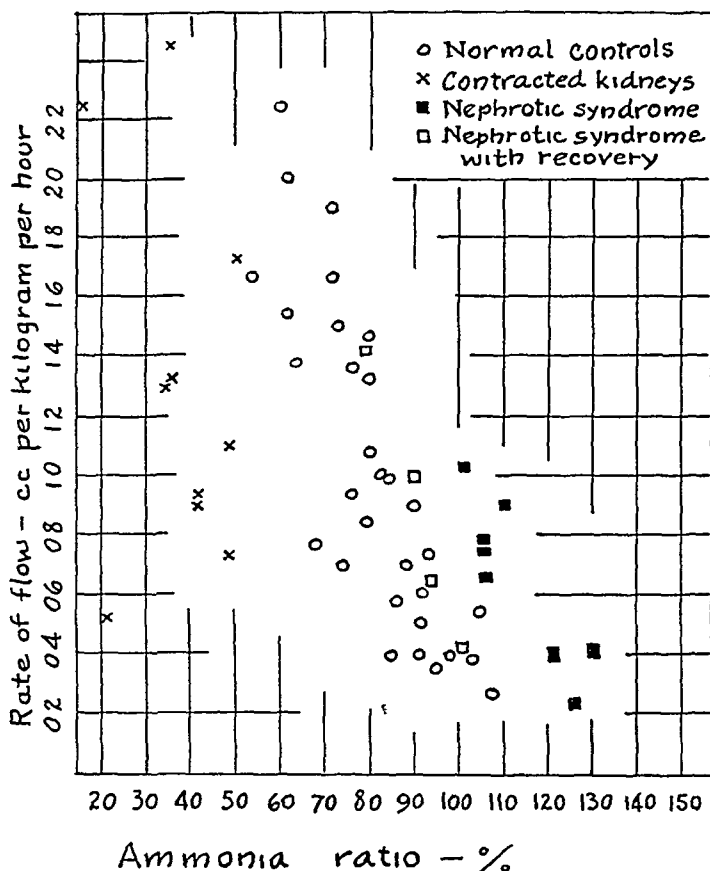


Chart showing the relation between excess acid, production of ammonia and rate of flow of urine in health and in certain types of nephritis.

At first glance these results appear to offer nothing more than confirmation of other studies showing "poor" production of ammonia in advanced nephritis. Thus, Van Slyke and his associates⁴ observed low ratios for $\frac{\text{ammonia}}{\text{titratable acidity}}$ and Magnus-Levy⁵ observed low ratios for $\frac{\text{ammonia}}{\text{total nitrogen}}$.

4 Van Slyke D D, Linder, G C, Hiller, A, Leiter, L, and McIntosh, J F. The Excretion of Ammonia and Titratable Acid in Nephritis, J Clin Investigation 2 255 (Feb) 1926.

5 Magnus-Levy, A. Das Ammoniak bei der Nephrose, Ztschr f klin Med 112 256, 1930.

However, it is rather obvious that the passing of a given volume of urine through the renal remnant of a nephritic patient requires a much greater speed than would be required for it to pass through a normal kidney with many more tubules. It is not unlikely, therefore, that an expression for approximate tubular rate of flow, if such could be obtained, would throw the nephritic ratios up into the normal zone.

This suggestion that the epithelium of the renal remnant in advanced nephritis is functioning in a normal manner demands a review of other evidence available. The manner of resorption of threshold material is of particular interest.

One of the characteristic findings with the destruction of much renal parenchyma is an increase in the urinary volume, particularly of the night portion. The explanation of this phenomenon may be that

TABLE 2—*Ammonia Ratios for Subjects with Contracted Kidneys*

Sub ject	Date	Chlo rine	Sul fate	Phos phate	Strong Or ganic Acid	Fixed Base	Excess Acid	Am monia	Ratio, %	Rate of Flow	Nonpro tein Nitro gen	Comments
T O	10/ 5/34	4 20	0 55	0 60	0 69	4 26	1 78	0 87	49	1 10	132	
G O	3/26/35	11 50	1 61	1 19	2 32	11 97	4 65	1 95	42	0 93		
	3/27/35	14 32	0 50	1 17	2 03	14 00	4 02	1 97	49	0 73	78	
N T	12/ 1/34	2 44	1 14	0 95	1 78	4 21	2 13	0 75	35	2 44	67	
F H	4/15/35	3 58	1 10	1 80	1 46	6 46	1 48	0 76	51	1 72	83	
H D	4/16/35	6 76	1 13	1 03	2 18	8 91	2 19	0 92	42	0 89	108	
T P	4/ 6/35	10 37	1 34	2 10	2 83	15 25	1 39	0 52	37	1 35		Pernicious anemia and nephritis
S D	10/27/36	5 66	2 02	0 61	1 78	8 06	2 01	0 42	21	0 57	110	
M M	11/ 5/36	7 14	1 22	0 51	1 93	8 53	2 32	0 80	34	1 24	90	
R W	11/12/36	7 13	1 56	0 69	1 52	9 07	1 85	0 33	18	2 23	120	

surviving glomeruli carry on compensatory overactivity and form an abnormal quantity of filtrate, then with an increased rate of flow through the tubules, more water escapes, because of the mechanical handicap to resorption, than would normally be the case. The hypertrophied appearance of surviving glomeruli and the dilatation of surviving tubules give evidence in favor of this suggestion.

Resorption of dextrose is practically unimpaired even in advanced nephritis.

Functional activity in resorption of chloride is best judged by the level maintained in the body fluids. The chloride content of the plasma in nephritis is low as a result of vomiting and at times from other causes, but in the absence of vomiting it is not usually low.⁶

6 Atchley, D W, and Benedict, E M. Serum Electrolyte Studies in Normal and Pathological Conditions. Pneumonia, Renal Edema, Cardiac Edema, Uremic and Diabetic Acidosis, *J Clin Investigation* **9** 265 (Oct) 1930. Greene, C H, Wakefield, E G, Power, M H, and Keith, N M. The Electrolyte Distribution and the Acid-Base Equilibrium in the Serum in Cases of Nephritis and Nephritic Acidosis, *Biochem J* **26** 1377, 1932. Briggs^{1a}

Resorption of fixed base, like resorption of water, is not quite perfect. Even in the absence of vomiting, the level of fixed base in the plasma is found to be most frequently between 145 and 150 milliequivalents per liter,⁶ whereas in health the fluctuations are most frequently between 150 and 155 milliequivalents per liter. In a previous publication¹ it was pointed out that this slight defect in resorption of fixed base might well be a diuretic effect, since diuresis always causes the waste of some fixed base.

It appears then, so far as resorption of threshold material is concerned, that there is no good evidence of impaired functional activity of the renal epithelium in this type of nephritis.

This conclusion should not be surprising, for each surviving tubule carries the burden of resorbing the threshold material filtered by only a single glomerulus. And a good state of nutrition should be preserved in the tubule so long as the circulation in the glomerulus is adequate for filtration.

The one defect which does exist, the excessive rate of flow, accounts for the slightly impaired resorption of water and fixed base and also for the low ammonia ratios. Surely it is an unnecessary assumption to attribute the slightly impaired conservation of fixed base in nephritis to the "poor" production of ammonia by the kidneys.

Tubular Function in Patients with the Nephrotic Syndrome—In contrast to the low ratios obtained for patients with contracted kidneys are the high ratios for those with the nephrotic syndrome (table 3). The rates of flow are observed to be low, but not lower than for some of the normal subjects with restriction of fluid.

These high ratios for nephrosis consequently fall to the right of the normal zone on the chart. This is the zone of excessive functional response. Ratios from these same subjects after recovery are observed to fall within the normal zone.

Studies of the ratio $\frac{\text{ammonia}}{\text{titratable acidity}}$ have not brought out any abnormality of secretion of ammonia in the nephrotic syndrome.³ Magnus-Levy⁵ has, however, observed in nephrosis high ratios for $\frac{\text{ammonia}}{\text{total nitrogen}}$ in the urine. And these results were thought by him to indicate that the kidney in nephrosis responds as usual to metabolic changes, but because of a state of irritation, an overproduction of ammonia results.

The interpretation which I have offered is much the same as that of Magnus-Levy. It is suggested that the tubular epithelium in nephrosis responds as in health to excess strong acid, but possibly it responds also to weak organic acid, because of a state of irritation.

The notion that cells with so-called degenerative changes, such as are observed in the tubular epithelium in nephrosis, might function with excessive activity is of course not a new one, cytologists from

time to time have called attention to this possibility.⁷ Sufficient consideration has not, however, been given to the possible clinical application of this conception.

The nephrotic syndrome is characterized clinically by scanty urine and the development of edema without retention of waste substances. The chief cause of the edema appears to be albuminuria, with resulting depletion of the protein content of the plasma. However, these patients may, without any changes in diet or medication or detectable change in the protein content of the plasma, show marked fluctuations in water balance. Such observations suggest the possibility of some other renal factor aside from that which permits albuminuria.

TABLE 3—*Ammonia Ratios for Subjects with Nephrosis*

Sub ject	Date	Chlo rine	Sul fate	Phos- phate	Strong Or Acid	Fixed Base	Excess Acid	Am monia	Ratio, %	Rate of Flow	Comments
W H	9/18/34	3.55	1.51	1.85	1.75	4.68	3.98	4.97	125	0.22	Nephrotic syndrome, chronic hemorrhagic nephritis
	9/22/34	2.44	2.49	1.24	1.61	5.04	2.74	3.32	121	0.40	
	12/13/34	9.85	1.09	2.27	2.32	7.08	8.45	9.34	110	0.91	Much less edema, ratio still high
	12/24/34	9.79	0.41	0.96	2.68	9.88	3.96	3.72	94	0.65	Free from edema normal ratios
	12/26/34	11.60	0.52	1.22	3.38	12.59	4.13	4.17	101	0.42	
D B	10/15/34	5.00	12.10	3.30	4.20	15.62	8.98	11.18	130	0.42	Nephrosis, otitis media
M D	11/ 9/34	9.12	5.25	4.24	2.62	12.00	9.23	9.75	106	0.79	Nephrosis, maxillary sinusitis
	12/29/34	15.70	2.24	2.99	3.24	19.90	4.27	3.82	90	1.00	Free from edema
E K	9/23/35	1.06	9.48	7.72	6.14	3.31	21.09	22.60	107	0.67	Nephrosis, tonsillitis sinusitis
	9/30/35	0.78	13.72	7.71	6.32	5.85	21.68	23.20	107	0.78	
	10/ 4/35	26.90	3.60	3.25	3.03	16.76	20.02	20.63	102	1.25	
	1/30/36	14.78	4.73	4.61	3.46	15.98	11.60	9.14	79	1.41	Nearly free from edema

Studies of urea clearance⁸ indicate that glomerular filtration may remain normal throughout the course of true nephrosis and that it is usually normal in the early edematous stages of the nephrotic syndrome of hemorrhagic nephritis.

The association of normal glomerular filtration with scanty urine is difficult to explain except on a basis of excessive tubular resorption. It has been suggested⁹ that degenerative changes in the tubules might

7 Oliver, Jean. A Further Study of the Regenerated Epithelium in Chronic Uranium Nephritis, *J. Exper. Med.* **23** 301 (March) 1916.

8 Van Slyke, D. D., Stillman, E., Ehrich, W., McIntosh, J. F., Leiter, L., Moller, E., MacKay, E. M., Hannon, E. R., Moore, N. S., and Johnston, C. Observations on the Courses of Different Types of Bright's Disease, and on the Resultant Changes in Renal Anatomy, *Medicine* **9** 257, 1930.

9 Cushing, A. R. *The Secretion of the Urine*, ed. 2, London, Longmans, Green & Co., 1926.

result in the loss of integrity for separation of threshold substances and permit back-diffusion of filtrate. Such a circumstance, however, could not account for the scanty urine in nephrosis, for the result would be the same as from diminished glomerular filtration—imperfect excretion of urea and other waste material, which does not occur.

Certainly the simplest and most consistent explanation assumes only what is suggested by the high ammonia ratios: excessive resorption of the threshold substances. The abnormal return of water and sodium salts to the body therefore provides a contributory cause for edema in the nephrotic syndrome.

SUMMARY AND CONCLUSIONS

Additional observations have been made showing the parallelism between ammonia and excess of acid over fixed base secreted in the urine.

It has been observed that the ratio of ammonia to excess acid is influenced by the rate of flow of urine through the tubules in a manner which is in harmony with my stimulus-response view.

From this point of view the ammonia ratio has been studied in certain types of nephritis as an index of functional activity of the renal epithelium.

In attempting to interpret the results it has been concluded that surviving epithelium of contracted kidneys may function in a fairly normal manner, that the high ratios observed in the nephrotic syndrome are best explained on a basis of excessive functional activity, due to a state of irritation, and that excessive resorption of water and sodium salts may be a contributory factor in the production of edema.

THALAMIC SYNDROME

SYNDROME OF THE POSTERIOR CEREBRAL ARTERY, A REVIEW

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BALTIMORE

The thalamic syndrome was first described by Dejerine and Egger¹ in 1903. Perhaps the subject can best be introduced by a description of the first classic case.

Early one spring morning in the year 1902 an elderly woman named Madame Jossaume ate breakfast with her usual relish. Afterward she sat back and perhaps mused over some of the events of her seventy-six years of life. Suddenly she felt dizzy. She fell to her knees, and everything seemed to swim about her. Then she began to vomit violently. She did not faint but was unable to get up without help. The family put her to bed. She was seized with an imperative desire to micturate without being able to do so. She tried to move her extremities but found that her left arm and leg were leaden and inert.

Fifteen days later the paralysis began to disappear, and soon Madame Jossaume could move her arms and legs almost as well as ever. She was at all times able to show her teeth, close her eyes and wrinkle her forehead. Her mouth never deviated to one side or the other. However, she was far from comfortable. The urinary retention had been succeeded by frequent irresistible calls to micturate. Furthermore, since her attack she had been tormented day and night by sharp continuous pains over the left side of the face, radiating down the left arm and over the whole left side of the body. When the pain was of greatest severity, she felt as though her left eye were being gouged out and torn from its socket. Intense burning and crawling sensations passed over the left temple, up the left ear and the left nostril and over the left half of the tongue. The illness began in April. In July the patient was suffering as much as ever, so she was taken to the Salpêtrière Hospital in Paris, where she was first seen by Dejerine.

"In spite of her seventy-six years," reads his note, "the patient shows no signs of senility." He began his examination by testing touch perception over her left hand with a water-color brush. She did not feel it at all. He tried various parts of her hand and the lower part of her forearm. Still no response! He moved up her arm, and there was now a faint perception of touch. There was hypesthesia of the arm, which diminished as the shoulder was approached. A corresponding state of affairs was found in the left foot and leg. The patient was unable to feel the brush on the left half of the face. The mucous membrane on the left side of the mouth, palate, pharynx and tongue was hypesthetic, and the same was true of the cornea and conjunctiva of the left eye.

Armed with a pin, Dejerine now explored his patient's sensibility to pain. Apparently some one had tried this immediately after her attack, three months

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1 Dejerine, J, and Egger, M. Contribution a l'étude de la physiologie pathologique de l'incoordination motrice, *Rev. neurol.* **11** 397, 1903

previously. At that time the pinprick elicited dysesthesia, creeping, crawling and other disagreeable sensations over the left half of the body but no localized sensation of pain at the point stimulated. The patient, however, felt Professor Dejerine's pinpricks for what they were, though the sensation was less sharp over the hand and foot than over the more proximal portions of the extremities. It is interesting here in the light of later work to mark well that no mention is made of any change in the threshold to pain. Furthermore, once the threshold was overcome (regardless of whether or not it was raised), the patient did not experience dysesthesia of a violence out of proportion to the stimulus, rather she felt the pinprick less sharply than on the good side.

Dejerine tried the effect of a warm stimulus (50 C) over the same areas and noted that the trunk and face were more sensitive to heat than the extremities. He apparently based this finding on a lag in response of fifteen seconds over the hand and of from fifteen to twenty-five seconds over the foot. On the forearm the delay was only three or four seconds, and over the arm and thigh the stimulus was felt immediately, although not as intensely as on the right side. He further observed that although the left side of the face was hypesthetic to heat it was hyperesthetic to cold. He did not, however, give details.

Madame Jossaume was barely able to feel pressure on her fingers, though as it was applied to more proximal portions of her arm she could feel it better. When the tuning fork was placed on bony prominences of the abnormal side of the body, she felt no vibration but instead complained of an intense burning sensation, even over those parts where anesthesia to heat had been most marked.

Investigation of the sense of limb position gave striking results. Apparently the patient had not the remotest idea that the position of the arm was changed, whether the joints were flexed, extended, abducted, adducted, rotated, pronated or supinated. The loss of the sense of passive movement in the leg was serious but not as profound. She knew, for instance, that her toes were being moved, but she could not tell in what direction.

Astereognosis of the left hand was complete. The patient was unable to recognize either the form or the physical properties of objects placed in her hand and could not name the objects. She had completely lost her sense of differences in weight.

Passing now to a review of the motor system, Dejerine found that all the movements of the extremities were entirely preserved. The muscles had not suffered either contracture or loss of tone. Muscle strength, however, was considerably weakened in both the left arm and the left leg. There was slight paralysis of the left side of the mouth but no evidence that emotional mimicry was in any way affected.

The ankle and patellar tendon reflexes were exaggerated on both sides but more so on the left. The deep reflexes in the arms were equal on the two sides. There was no true Babinski sign on either side, although plantar stimulation resulted in dorsal flexion of both feet.

Dejerine noticed that from time to time the patient's left arm was agitated by a choreic tremor, consisting of small movements of pronation and supination and of flexion and extension of the arm, hand and fingers. Conversational allusion to her arm caused the tremor to appear and the patient was unable to control it. Dejerine found that the only way to stop the tremor was to divert her attention. A certain awkwardness of the left side was manifest, but after some hesitation she was able to touch her nose with her eyes closed. Some diminution of hearing was noted on the left and a sensation of dryness of the mouth on the left.

These are the facts in the order that Dejerine uncovered them. Another similar case was brought to his attention, and he reported both at a meeting of the Paris Neurologic Society in April 1903. His diagnosis was lesion of the optic thalamus. A few months later Thomas and Chuay (1904) presented two cases in which there were almost identical symptoms and proposed the thalamic syndrome.

A year later Madame Jossaume died. The autopsy must have aroused considerable interest. The meninges and hemispheres were normal. Examination of the brain stem revealed that the right pyramid was larger than the left. The knife was then passed through the brain in a horizontal plane from the frontal to the occipital lobe, just grazing the uppermost part of the corpus striatum and thalamus. When the top section of the brain was lifted off, a brownish-yellowish area, about as large as a hazelnut was revealed in the posterior and lateral part of the right thalamus.

In 1906 Dejerine and Roussy² described a symptom complex dependent on a lesion exactly localized in the optic thalamus. The hemiplegia develops in a mild manner. If consciousness is lost at all it is only for a short time. The paralysis is always slight, without the development of contracture, and is rapidly regressive. The ability to move the extremities is usually restored quickly. Hypotonicity of the muscles and diminution of muscular strength are noted. The deep reflexes are a little exaggerated, but there is seldom a Babinski sign.

Mild hemiataxia is considered to be dependent on loss of sensation and related to more or less complete astereognosis. Hemichorea and athetosis are frequent. Tremor was observed in one case.

The sensory changes are both subjective and objective. There is superficial anesthesia which is accompanied with persistent and marked loss of deep sensation. Touch, pain and temperature sensibilities are modified in a way similar to that found with lesions of the internal capsule. The change extends for 1 or 2 cm over on the sound side of the body. There are astereognosis and loss of position sense.

The severe pain on the paretic side is persistent, paroxysmal and often intolerable and does not yield to drugs. It involves the whole side of the body, including the face and trunk. The pain is spontaneous or is evoked by contact with heat or especially with cold, by passive movement of the extremity or by deep pressure.

Two symptoms of the second order are sometimes observed, rectal and vesical tenesmus and hemianopia.

In two cases abnormalities of the functions of the bowel and bladder formed outstanding symptoms. The disturbances of micturition appear at the beginning of the illness. There may be retention

² Dejerine, J., and Roussy, G. Le syndrome thalamique, *Rev. neurol.* **14** 521, 1906.

with tenesmus which is followed by frequent painful micturition. In the case just described the patient felt an imperative need to micturate, without being able to satisfy it. The tenesmus was painful, with radiation into the lower portion of the abdomen and perineum. The vesical pain persisted with marked intensity for two months. Gradually the retention disappeared, to be replaced by imperative micturition.

Vasomotor changes are marked. Early in the disease the extremities are red and congested, later they are cold and blue. The fingers are cyanotic. Trophic changes also are present in the hands and feet.

The patients sometimes have difficulty in swallowing owing to the decrease of salivary secretions and dryness of the mouth on the affected side.

Dejerine gave his pathologic material to Roussy for microscopic study, and in 1907 Roussy³ published his famous monograph on the optic thalamus. He had performed numerous animal experiments testing the effect of artificial thalamic lesions and had carefully studied serial sections of the brains of five patients, including that of Madame Jossaume. He found that the clinical symptoms in these different cases were dependent on lesions localized in exactly the same region of the thalamus. He not only determined the precise location of the central lesion but studied the associated degeneration in the tracts.

In summing up the Jossaume case he pointed out that the clinical signs of deep and superficial anesthesia on the left, rapidly regressive hemiplegia, slight hemiataxia, astereognosis and sharp, stubborn pain on the paralyzed side corresponded anatomically with a primary lesion of the thalamus entirely destroying the posterior third of the lateral nucleus, encroaching mesially on the medial and central median nuclei, on the pulvinar behind and laterally, cutting into the posterior limb of the internal capsule and the posterior portion of the lenticular nucleus. "We believe," said Roussy, "that with the support of these findings there is now good reason to admit the existence of a new clinical syndrome produced by lesions in the optic thalamus, the thalamic syndrome."

He stated the five cardinal points of the new syndrome as follows:

- 1 Loss of superficial and particularly deep sensation on the side of the body opposite the lesion
- 2 Transient hemiplegia
- 3 Slight ataxia on the affected side of the body, with some astereognosis
- 4 Intense, stubborn pain on the affected side, not yielding to any treatment
- 5 Choreo-athetoid movements of the paralyzed side

3 Roussy, G. *La couche optique. Le syndrome thalamique*, Paris, G. Steinhil, 1907.

Roussy finally concluded that although the sensory disturbances can be referred to thalamic loss the motor symptoms develop because in the vast majority of cases the areas of softening or of hemorrhage do not remain localized in the thalamus but invade neighboring structures, such as the internal capsule. Hemiataxia is an exception, as it was thought by Dejerine and Roussy to result from the loss of the sense of limb position and hence could be related to the thalamic lesion. Hemianopia, which is sometimes present in cases of thalamic involvement, is also a result of encroachment on the optic tract, optic radiations, optic geniculate body or perhaps, even more often, the visual projection area in the cerebral cortex.

Roussy built the syndrome on such a firm pathologic basis that subsequent work has consisted chiefly of interpretation and analysis of symptoms. Little more is now known about the thalamus than he described, but more of the thalamic connections have been worked out, more is known of the blood supply of the region and new theories of sensation have been developed.

Across the channel Henry Head read Roussy's reports and was impressed by the accounts of dysesthesia in some of the patients. Madame Jossaume showed the response of dysesthesia soon after her trouble began. Another patient could not feel pinpricks on her arms and legs well but instead felt a painful, numb sensation which was not at all localized at the point of stimulus. In one of Thomas' cases a pinprick on the finger was felt on a neighboring finger, and a prick on the ear was felt on the cheek, in some cases the point of perception being 10 cm. away from the real stimulus.

Head had vivid memories of how his own arm had felt when the superficial radial nerve was regenerating. In fact, the dysesthesia and loss of localization of the French patients with the thalamic syndrome sounded much like his own description of protopathic sensation. He had said that in the stage of protopathic sensibility the punctate end-organs have a high threshold and respond in an all or nothing manner. Sensation radiates widely and is even referred to remote areas. Localization is deficient. In addition, the pleasure-pain tone accompanying sensation is altered so that the painful sensations have a peculiar intense quality and pleasurable ones a corresponding accretion of pleasure tone. An area endowed with protopathic sensibility alone is in a state of defective sensibility, for all stimuli the threshold is high, and yet the response is peculiarly vivid, so much so that the state is commonly described as one of hyperalgesia.

Head⁴ found a patient who showed Roussy's five points, with clear signs of dysesthesia. When a pin was lightly dragged across her face

4 Head, H. *Studies in Neurology*, London, Hodder & Stoughton, 1920.

or trunk, she exhibited intense discomfort when the midline was passed, not only did she cry out that it hurt her more, but her face became contorted with pain. However, she insisted that, although the stimulus was more painful, it was "less plain" and "less sharp" than over normal parts. The prick was less distinct but hurt more. Head said

This hyperalgesia or over-reaction would seem to point to a lowered threshold to the prick of a pin. But measured stimulation with the spring algometer shows that if anything the threshold is a little raised, she never responded with certainty over the abnormal (left) half of her body to a stimulus which can evoke a sensation of pricking on similar normal parts to the right of the middle line, the same stimulations, provided they are sufficiently strong to cause pain, produce a more uncomfortable sensation on the abnormal side.

The term overreaction is of special significance, because Head said he believed that overreaction is characteristic of certain lesions in the thalamus. The mere loss of sensation on one side of the body could be produced by interference with sensory impulses as they enter the optic thalamus or as they pass to the cortex by way of the internal capsule. Complete destruction of the thalamus would result in hemianesthesia, but then there would be neither spontaneous pain nor the overreaction.

In these cases of overreaction Head found that pressure is particularly liable to produce distress and increased reaction on the affected side. This increased reaction is frequently, though not necessarily, associated with a lowering of the threshold. When the pressure is exerted there is something terrifying about the crushing sensation, especially when a bone is pressed on. The condition is less a pain than an unbearable and distressing sensation, and in this way differs profoundly from the prick of a sharp point.

Thermal sensibility may be actually diminished so that the degrees of heat and cold belonging to the middle of the thermal scale may be appreciated as less hot or less cold than they would be on the normal side of the body. As soon as the extremes above 47 or below 26 C are approached, the sensations experienced are those of greater heat and greater cold on the affected half of the body. The sensations are not necessarily those of excessive heat or cold, but the patient may complain of disagreeable boring or pricking sensations.

Head found also that sensations normally accompanied with a pleasurable feeling produced an overreaction. One patient could not recognize any thermal stimulation as such, and yet over the affected half of the chest large tubes containing water at from 38 to 48 C evoked intense pleasure. This was shown not only by the expression of the woman's face but by her exclamations, "Oh! that's lovely, its so soothing so very pleasant!" In one case a tube containing water at 38 C when applied to the normal palm was said to be warm but the

patient cried out with pleasure when it was placed in the affected hand. His face broke into smiles, and he said, "Oh! that's exquisite. That's real pleasant."

Head was the first to notice that in states of emotion the two sides of the body react differently in cases of thalamic involvement. Music is peculiarly liable to evoke a different reaction on the two halves of the body. One patient was unable to go to his place of worship because he could not bear the effect of the hymns on his affected side, and his son noticed that his father constantly rubbed the affected hand during the singing. A highly educated patient confessed that he had become more amorous since the attack, which had rendered the right half of his body more responsive to pleasant and unpleasant stimuli. He said, "I crave to place my right hand on the soft skin of a woman. It's my right hand that wants the consolation. I seem to crave for sympathy on my right side." Finally he said, "My right hand seems to be more artistic."

Head was convinced that protopathic sensibility for various reasons was not merely a temporary expression of regenerating sensory nerve fibers but a distinct functional entity normally held in selective control by the epicritic system. Protopathic sensibility is controlled through the thalamus, epicritic, through the cerebral cortex. The characteristic lesions producing the thalamic syndrome lie in the lateral part of the thalamus, where the thalamic radiation passes to the cortex and the corticothalamic fibers enter the thalamus. Head regarded the symptoms of overreaction and spontaneous pain as release phenomena. Whether or not one accepts Head's theories of protopathic and epicritic sensation, the idea of release phenomena has strong anatomic justification.

Head pointed out that the optic thalamus as an anatomic structure is an extremely complex portion of the brain which not only contains the terminal center for certain aspects of sensation but plays a three-fold part in the fate of sensory impulses. First, it contains the termination of all secondary sensory fibers. Here the sensory impulses are grouped afresh and redistributed in two directions, to the cerebral cortex and to the gray matter of the thalamus itself. Second, it contains a mass of gray matter, the essential organ of the thalamus, which forms the center for certain fundamental aspects of sensation. It is complementary to the sensory cortex and exercises different functions in the production of sensation. Lastly, the lateral part of the thalamus is an organ through which the cortex can influence the essential thalamic centers, controlling and checking their activity.

The most remarkable feature in cases of thalamic involvement is not loss of sensation but an excessive response to affective stimuli. This may be accompanied with much or with little loss of sensation,

but the extent of this loss, according to Head, bears no relation to the amount of the overreaction to painful stimuli. It is necessary only that sufficient sensory impulses, capable of exciting discomfort, should be able to reach the consciousness.

The pains and uncomfortable paresthesia which occur in these cases have been explained by some observers as due to irritation. Now, all vascular lesions of the nervous system notoriously tend to produce the greatest disturbances of sensation at the time when they occur, the subsequent progress of the disease always shows a certain amount of recovery. But in the group of cases of thalamic involvement the pain and overreaction come on during the stage of recovery of function. They may appear a considerable period after the stroke and last unaltered for years. The response to pleasurable stimuli is also increased in some of these cases, a condition incompatible with the existence of an irritative lesion which evokes pain.

It is well known that a lesion of the cerebral motor cortex produces not only a loss of voluntary movement but also a positive effect in the increased tone of the extremities. The same condition is revealed on the sensory side in cases of thalamic disease accompanied with excessive response to peripheral stimuli. Since the paths from the cerebral cortex to the thalamus come from all parts of the cortex, the functions they exercise cannot be removed by partial destruction of the cerebral hemispheres. The only method of releasing the optic thalamus from cortical influence is to destroy the lateral nucleus, in which the majority of the corticothalamic fibers seem to end.

All the stimuli which produce an excessive effect when the thalamus is freed from cortical control contain elements which can excite the essential center of this organ. The nearer a sensation approaches pure discomfort, the more certainly will the response be exaggerated on the affected side of the body. States of pleasure and stimuli such as warmth also may evoke excessive manifestations on the abnormal side. The activity of the essential thalamic center is mainly occupied with the affective side of the sensation. The feeling tone of somatic or visceral sensation is the product of thalamic activity. Since most stimuli which act on the body in daily life are noxious and contain a disagreeable element, most sensations experienced by a patient with a lesion of the optic thalamus are painful.

Holmes and Head⁵ (1911) stressed the development of deafness in a certain number of cases of the thalamic syndrome. The deafness was usually bilateral but greater on the affected side of the body. They described a case of their own in which deafness was a symptom and

⁵ Holmes G, and Head, H. A Case of Lesion of the Optic Thalamus with Autopsy. *Brain* **34** 225, 1911.

found reports of four others in the literature. There is sometimes associated an extreme susceptibility to loud sounds, which may actually become painful to the patient.

Earlier workers on the problem of the thalamic syndrome gave little attention to the motor side. Roussy and his immediate followers felt that the motor symptoms resulted from involvement of neighboring motor tracts rather than from the thalamic lesion itself. By 1925, when Hillemand⁶ published his thesis on the thalamic syndrome, the motor disturbances were given as much emphasis as the sensory disturbances.

The motor symptoms which are found in cases of the thalamic syndrome may be grouped for purposes of discussion under the three headings ataxia, contractures and abnormal movements. This leaves out of consideration the hemiparesis which is due to the spread of the lesion into the internal capsule or involvement of the cerebral peduncles. We wish to trace for a moment the different views in respect to these three motor abnormalities and their interrelations.

The first paper describing the thalamic syndrome, by Dejerine and Egger in 1903, laid stress on the motor incoordination. In fact, it was entitled "A Contribution to the Study of the Pathologic Physiology of Motor Incoordination. Ataxia of Peripheral Origin and Ataxia of Central Origin." The ataxia in the case of Madame Jossaume appeared to them to be the feature of her illness of greatest interest and significance. In this case they noticed decomposition of movement or asynergia. There was ataxia in the finger to nose test, associated with a tremulousness of movement. Dejerine compared the ataxia with that found in patients with tabes who had completely lost deep sensation in the arms. He observed that the tabetic ataxia was much more marked than that found in the patients with the thalamic syndrome. Deep sensation was greatly impaired in both cases. The difference lay, he believed, in the location of the lesion. In tabes the fibers mediating deep sensation are injured at the point where they enter the cord. Under these conditions they establish no reflex connections in the nervous system. In the thalamic syndrome only those fibers are injured which are destined to mediate conscious information concerning the position of the extremities. The proprioceptive pathways connecting with the brain stem and cerebellum, which control the postural reflex, are intact.

Later it became clear that many of the symptoms of ataxia seen in these patients are similar to those commonly related to cerebellar lesions. In many cases a diminution in tone can be demonstrated in

⁶ Hillemand, P. Contribution à l'étude des syndrômes de la région thalamique, Paris, Jouve & Cie, 1925.

the extremities, as well as intention tremor, ataxia and asynergia. The large efferent pathway from the cerebellum lies in the superior cerebellar peduncle. Many of these fibers end around cells in the red nucleus, but at least a third of the pathway passes forward to end in the thalamus. A lesion in the realm of the posterior cerebral artery may injure the fibers from the cerebellum to the thalamus. This may be a part of the typical thalamic syndrome. By means of perforating branches the posterior cerebral artery supplies also the capsule and cells of the red nucleus as far caudad as the oculomotor nucleus. A large proportion of the fibers of the cerebello-efferent system may thus be injured.

It appears then that at least two factors may operate in the production of ataxia. There may be loss of conscious information concerning the position of the extremities owing to injury of the proprioceptive pathway to the thalamus. The large pathway carrying impulses from the cerebellum to the thalamus or to the red nucleus may be involved.

Abnormal movements are usually observed in the extremities. It is difficult to classify abnormal movements, and those associated with the thalamic syndrome are of various types. Intention tremor often appears in the hand in the performance of the finger to nose test. The intention tremor is probably related to the injury of the cerebellar pathways.

Other patients show movements of the choreo-athetoid type. There is no adequate information concerning the lesions in the nervous system which produce this type of movement. Many investigators feel that these lesions are related to the basal ganglions or their projection systems. It is clear that after lesions of the subthalamic nucleus of Luys, unilateral abnormal movements of the extremities appear on the side of the body opposite the injury. They are choreo-athetoid in type. This condition is known as hemiballism. The premamillary and postmamillary branches of the posterior cerebral artery penetrate and supply a large portion of the subthalamic region. It may be involvement of this area which produces the choreo-athetoid movements. The movements may also in part be dependent on the loss of information concerning the position of the extremities.

The abnormal movements of the hand are exaggerated by changes in position or by exertion. They are increased also by activity of the other hand. In certain cases the abnormal hand tends to duplicate all the movements of the normal one. Thus, the abnormal hand may endeavor to help with fastening buttons and tying shoelaces and show all the movements of the normal hand, even though it is not intentionally used in the activity. In walking the hand is often extended

behind the body, with the arm in maximal internal rotation so that the palm turns backward

The contracture seen in cases of the thalamic syndrome is entirely different from that encountered in hemiplegia. It is an active living contracture which varies in intensity from day to day and increases with voluntary movement.

Hillemand said that by means of the contracture it is usually possible to recognize cases of the thalamic syndrome. The upper extremity is much more involved than the lower. There is strong flexion at the elbow, and the wrist is slightly flexed and pronated. The hand is rarely closed. The fingers are straight. Often the metacarpophalangeal joint is moderately flexed, while the second and third phalanges are completely extended. There may be unusual adduction of the fingers so that they overlap. Sometimes the fingers are hyperextended at all joints, as in congenital athetosis. Vasomotor and trophic changes are marked in the hand. Indeed, the French authors speak of the "thalamic hand" as characteristic of the syndrome.

Although the arm appears to be in strong contracture, passive movement can be carried out easily, and the contracture seems to melt away. Movements are difficult because of poor coordination between the prime movers, synergist and antagonist muscles. The intention contracture, according to Hillemand, plays a large part in the production of the athetoid movement.

In summary, it is seen that the motor abnormalities are dependent on several possible factors. Owing to the incompleteness of knowledge of the physiology of abnormal movements in general, it is impossible at present to make a complete analysis. Moreover, the movements show a great variation in different cases of the thalamic syndrome dependent on the extent of the anatomic involvement. The two most important factors are the involvement of the efferent fibers of the cerebellum and the loss of information concerning the position of the extremities. These two abnormalities are present in all typical cases of the thalamic syndrome in which choreo-athetoid movements form a cardinal symptom. A third factor in the production of abnormal movements is the involvement of the area of the subthalamus by occlusion of perforating branches of the posterior cerebral artery. This subthalamic injury is inconstant and hence accessory to the typical picture.

The importance of the vasomotor and trophic changes in the thalamic syndrome has not been sufficiently emphasized. Although the pain may be late in appearance, a case of the thalamic syndrome may be recognized early by the unusual vasomotor changes on the paralyzed side. There is great swelling of the extremities, which are warm to the

touch. This may persist for weeks and then disappear. The skin remains thin and shiny. Scaling of the epidermis appears in the region of the hand, and trophic changes are noted in the nails. It is difficult to understand the mechanism of the vasomotor change. Is the reflex arc controlling the tone of the smooth muscle of the vessel walls injured on its sensory side? Or is there some injury of a local mechanism in the region of the thalamus controlling the smooth muscle of the blood vessels?

It must always be remembered that the pain may appear to be localized in the abdominal viscera. We have seen recently a patient with thalamic pain who experienced severe discomfort in the upper portion of the abdomen, interpreted as due to a gastric ulcer. No abnormalities in the intestinal tract or in the abdominal cavity were observed at operation or at subsequent postmortem examination.

In several cases of the thalamic syndrome we have noticed that the pupils were of unequal sizes. The smaller pupil is found on the same side as the lesion in the brain, the larger, on the affected side of the body. The smaller pupil is the abnormal one. There is a pathway from the hypothalamus which controls the sympathetic innervation of the pupils and is uncrossed. After injury to this pathway the pupil becomes smaller on the side of the lesion.

The whole subject of the thalamic syndrome became confused in the years which followed the publication of Dejerine's first article. Hardly a volume of the *Revue neurologique* was published without two or three articles referring to the thalamic syndrome. Patients were described with various degrees of sensory involvement and motor disturbances. A subthalamic syndrome was formulated. It remained for Foix and Masson⁷ (1923) and Foix and Hillemand⁸ (1925) to clarify the whole subject by pointing out the relationship between the physiologic disturbances and the vascular lesions. Since the vascular involvement has to do almost entirely with the posterior cerebral artery, Hillemand described the syndrome of the posterior cerebral artery. He studied carefully the branches of the artery and their relationship to the anatomic structures. The abnormalities seen in these patients become understandable when the anatomy and physiology of the portions of the brain supplied by the different branches of the posterior cerebral artery are considered.

While thrombosis of the posterior cerebral artery is less common than thrombosis of the middle cerebral, it occurs frequently. The

7 FOIX, C., and MASSON, A. Le syndrome de l'artere cerebrale posterieure, *Presse med* **31** 361, 1923.

8 FOIX, C., and HILLEMAND, P. Les syndromes de la region thalamique, *Presse med* **33** 113 1925.

complexity of the area supplied explains its clinical interest. It gives branches to the peduncular region, the subthalamic and thalamic areas, the visual projection area in the cerebral cortex, the splenium of the corpus callosum and the inferior and mesial surfaces of the temporal lobe. The posterior choroid artery supplies large areas adjacent to the lateral ventricles.

This great number of branches explains the possibility of many symptoms which form part of a great syndrome. One sees it from time to time completely realized. It is important to understand that thrombosis of a single branch of one of the great cerebral arteries seldom occurs without some impairment of nutrition throughout the whole course of the artery. Any sclerotic process involves the artery as a whole. Sclerotic patches appear in its walls at the base of the brain. They encroach on the lumen of the vessels, decreasing the flow of blood to the whole area which it supplies. Smaller branches may become completely occluded, giving rise to focal symptoms. Other neighboring areas suffer from impairment of circulation.

This explains the symptoms often associated with the thalamic syndrome. There is seldom a completely isolated lesion of the thalamus, subthalamus, calcarine area or inferior surface of the brain. Instead, there are multiple foci of softening dependent on the breaking down of nerve tissue due to loss of nutrition. This gives diverse symptoms owing to involvement of gray and white matter. If symptoms of one type predominate and appear in frequent association, they form the background of the whole picture. This is true of the thalamic syndrome. The vascular lesion may occur in the trunk of origin of the posterior cerebral artery, during its course or in any of the branches. Certain branches supply areas which are so important that a minute lesion gives rise to grave symptoms.

The artery arises from a bifurcation of the basilar trunk, encircles the cerebral peduncle and travels to the level of the optic colliculi. It then crosses to the temporal lobe, where it lies on the internal border of its inferior face and divides into three terminal branches. The anterior branch by a recurrent path turns to the anterior pole of the temporal lobe. The postero-external branch travels over the inferior surface of the temporo-occipital lobe, supplying the fusiform lobule and the last external temporal convolution. The postero-internal branch is the artery to the calcarine area. It lies buried in the calcarine fissure. This branch supplies the internal face of the temporal lobe. It seems to be a continuation of the main trunk. In summary, the anterior or anterior temporal branch supplies the anterior part of the inferior temporal gyrus, hippocampal gyrus and occipitotemporal gyrus. The postero-external or posterotemporal branch supplies the posterior part

of the inferior temporal, hippocampal and occipitotemporal gyri and also the anterior part of the lingual gyrus. The calcarine portion of the postero-internal branch supplies the posterior part of the lingual gyrus and the inferior half of the cuneus. It also sends blood to the quadrate lobe and the splenium of the corpus callosum.

The posterior cerebral artery is seldom occluded at its origin. There is an anastomosis by means of the posterior communicating arteries with the circle of Willis. This connection is of variable importance. Sometimes the posterior communicating artery is a large trunk. There is also considerable anastomosis with neighboring arteries in the peripheral area. Softening in the region of the posterior cerebral artery is usually subtotal. The peduncular area tends to be excluded.

The blood supply of the brain stem at the level of the cerebral peduncles, according to Foix and Hillemand, simulates the same general pattern seen at lower levels in the medulla (fig 1 *A*). There are branches to midline structures, short circumflex and long circumflex arteries. Thus, in the medulla there are short branches entering the midventral area and supplying structures on each side of the midline as far dorsal as the fourth ventricle or the aqueduct of Sylvius. The short circumflex branches supply a more lateral portion of the brain stem. The long circumflex branches in the medulla are the cerebellar arteries. They supply the most lateral portion of the brain stem.

In the peduncular region the quadrigeminal bodies simulate the long circumflex arteries (fig 1 *A*). They arise from the posterior cerebral artery before its anastomosis with the posterior communicating artery. Each quadrigeminal artery bifurcates into two branches, one to the optic and one to the acoustic colliculus.

The posterior choroid artery may arise separately from the posterior cerebral artery or by a common trunk with the quadrigeminal artery (fig 1 *A*). The posterior choroid artery gives off six or seven rami to the cerebral peduncles and afterward several short circumflex branches. There are several branches to the anterior part of the optic colliculi and one or two to the geniculate bodies. The posterior choroid artery also gives off one or two twigs to the splenium of the corpus callosum. Other branches from the posterior choroid artery are given off to the splenium from the lateral ventricle.

The main trunk of the posterior cerebral artery surrounds the cerebral peduncle and gives off several circumflex branches. The anterior choroid artery from the internal carotid artery swings backward and also gives off branches to the base of the peduncle.

The short, or paramedian, branches of the posterior cerebral artery have been described best by Hillemand. He divides them into two groups, depending on whether they are given off in front of or behind

the mamillary bodies (fig 1 *B*) Although the manner of origin of these branches shows considerable variation, the area supplied by them is constant

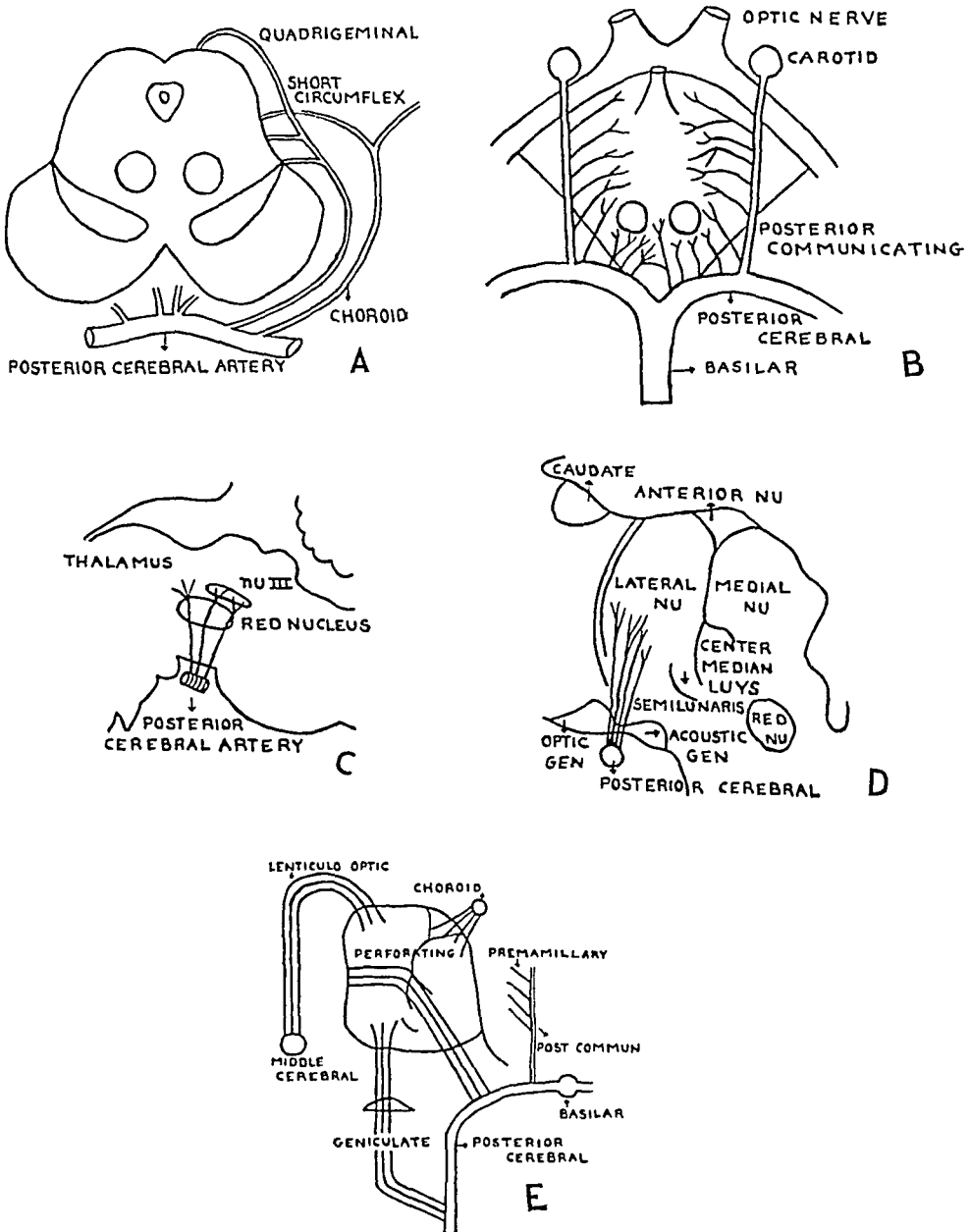


Fig 1—*A*, the blood supply of the region of the cerebral peduncles, showing the origin of the quadrigeminal and posterior choroid arteries from the posterior cerebral artery. The pattern of the blood supply to the brain stem is clearly shown. It consists of small branches supplying the midline structures, short circumflex and long circumflex branches. *B*, the premamillary and retromamillary arteries are given off from the posterior communicating and posterior cerebral arteries. *C*, the inferior group of retromamillary arteries given off from the posterior cerebral artery supply the anterior portion of the capsule of the red nucleus and the oculomotor nucleus. *D*, the geniculate branches arising from the posterior cerebral artery supply the lateral nucleus of the thalamus. Occlusion of these branches gives rise to the thalamic syndrome. *E*, diagram showing the blood supply of the thalamus.

The premamillary branches are given off from the posterior communicating and posterior cerebral arteries (fig 1 *B*). They are comprised of a dozen trunks of variable size. They usually arise separately at regular intervals, but in some cases they are given off from common trunks.

The retromamillary branches again form two separate groups (fig 1 *B* and *C*). The posterior, or peduncular, branches supply the areas on both sides between the cerebral peduncles (fig 1 *C*). They give blood to the region of the red nucleus as far caudad as the lower end of the oculomotor nucleus (fig 1 *C*). The anterior group supply the subthalamus and a portion of the thalamus itself (fig 1 *B*), they may be called the thalamoperforating arteries. Sometimes they are given off from a common trunk, but there are usually at least a dozen branches. They give blood to Forel's field and the retrothalamic groups of fibers. The thalamoperforating branches also supply a portion of the external nucleus of the thalamus as far as its lateral surface (fig 1 *E*).

The geniculate arteries are the most important branches of the posterior cerebral artery, as their occlusion gives rise to the typical thalamic syndrome (fig 1 *D* and *E*). They are given off at the point where the artery crosses from the brain stem to the inferior surface of the temporal lobe. There are five or six of these small arteries, usually arising separately. They penetrate the optic geniculate body vertically and supply the posterolateral part of the external nucleus of the thalamus, the antero-inferior part of the pulvinar, the internal part of the optic geniculate body and the external part of the acoustic geniculate body. They also supply the posterior portion of the internal capsule.

There remains but to describe the distribution of the posterior cerebral artery on the surface of the hemisphere (fig 2). It supplies all the inferior surface of the cortex and the inferior surface of the temporo-occipital area except for the anterior tip, which is supplied by the middle cerebral artery (fig 2 *A*). The area of the posterior cerebral artery extends on the external face of the hemisphere over the third and sometimes the second temporal convolution (fig 2 *B*). It supplies all the calcarine area, the mesial surface of the temporal lobe, part of the hippocampal gyrus and the splenium of the corpus callosum (fig 2 *C*).

The symptoms produced by occlusion of the cortical branches may be summarized briefly. There are two symptoms, hemianopia and alexia. Hemianopia is dependent on the destruction of the visual projection area around the calcarine fissure. In many cases of the thalamic syndrome the hemianopia is quadrantic, involving especially the upper quadrant. Most investigators believe that hemianopia when

present in cases of the thalamic lesion, is dependent on destruction of the calcarine area rather than of the optic tract, geniculate body or optic projection system. Aphasia, which is an almost pure alexia, is seen when the lesion occurs on the left side in right-handed persons. This is dependent on damage to the fibers in the splenium of the corpus callosum.

The relation of the choroid arteries to the thalamus is of considerable interest. Not only do they irrigate a large part of the dorso-lateral portion of the thalamus, but perforating branches from the anterior choroid artery penetrate the hypothalamus from below and may supply a ventrolateral portion of the lateral thalamic nucleus. In

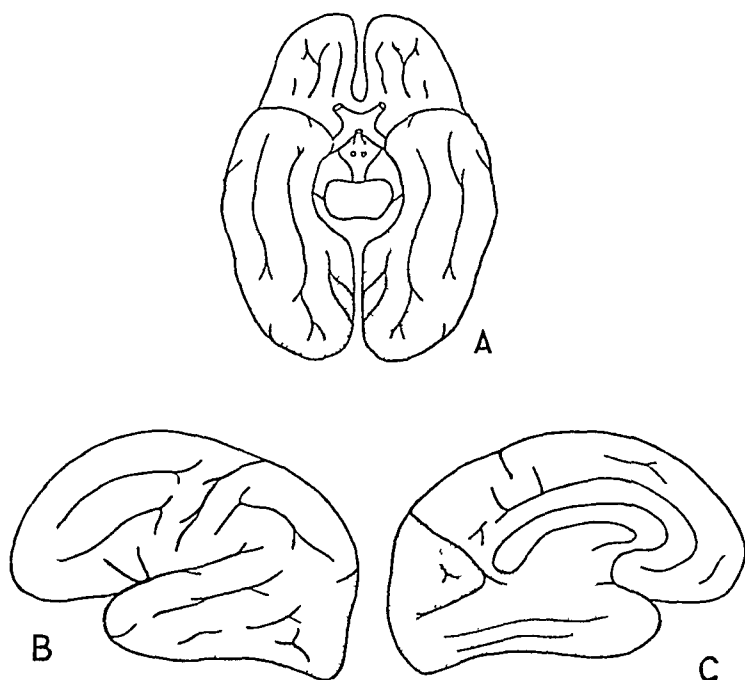


Fig 2—*A*, distribution of the posterior cerebral artery on the inferior surface of the brain. *B*, distribution of the posterior cerebral artery on the lateral surface of the brain. *C*, distribution of the posterior cerebral artery on the mesial surface of the brain, including the calcarine area.

their course over the dorsal surface of the thalamus the anterior and posterior choroid arteries lie in close approximation.

There are two posterior choroid arteries. They may arise separately or as a common trunk at the point where the posterior cerebral artery gives off the peduncular arteries. The principal choroid artery surrounds the peduncle, giving off six or seven branches to the cerebral peduncle. It also supplies some short circumflex branches. Other branches go to the anterior part of the optic colliculus and one or two to the corpus callosum, and then the main trunk irrigates the choroid plexus.

The accessory posterior choroid artery has a more limited territory. It runs to the lateral ventricle. There is a balance between the importance of these two posterior arteries.

The anterior choroid artery comes from far in front. It is situated first in front of and then outside the curve of the posterior cerebral artery. It turns dorsad over the cerebral peduncle, to which it furnishes numerous branches.

The anterior and posterior choroid arteries above the cerebral peduncle run almost parallel. The anterior is slightly above the posterior artery. They furnish branches to the posterior horn of the lateral ventricle and then describe a circle with the concavity anteriorly. At the point where this circle begins, a number of branches are given off to the posterior part of the pulvinar. The importance of these small branches merits the name of the pedicle of the pulvinar. They supply the postero-internal portion of the nucleus.

The anterior and posterior choroid arteries run over the superior and internal border of the thalamus in contact with the choroid plexus. A number of branches are given off to the thalamus which enter the superior surface.

With this survey of the branches of the posterior cerebral artery, it is best to turn next to the thalamus and consider with Hillebrand its complex blood supply (fig 1 *E*). It may be divided into five sources: (1) premamillary branches, (2) retromamillary branches, especially thalamoperforating, (3) geniculate arteries, (4) the posterior choroid artery from the posterior cerebral artery and the anterior choroid artery from the internal carotid artery, and (5) the lenticulo-optic artery from the middle cerebral artery.

The premamillary branches, like the retromamillary and geniculate arteries, are extremely small (fig 1 *B*). The most anterior of the premamillary arteries arise from the posterior communicating arteries and the caudal three or four from the posterior cerebral artery. They supply the anteroventral portion of the thalamus in its mesial portion.

The thalamoperforating branches of the retromamillary group supply the posteromedial portion of the thalamus and also a part of the external nucleus (fig 1 *B* and *E*).

The geniculate branches supply the postero-inferior portion of the external nucleus (fig 1 *D* and *E*). This area usually includes the part of the ventrolateral nuclei in which sensory projection fibers end, the semilunar nucleus and part of the central medial nucleus of Luys. They also supply the area where fibers from the cerebellum terminate. The area of this artery also includes a portion of the anterior end of the pulvinar and a portion of the geniculate body. The area of destruction appears larger in sections stained for cells than in those stained for myelin sheaths.

The anterior and posterior choroid arteries run in an almost parallel direction over the lateral surface of the thalamus and supply the upper and medial surface. They give off branches at intervals which plunge beneath the surface (fig 1 *E*). Large branches are given off to the pulvinar.

The lenticulo-optic artery, a branch of the middle cerebral artery, is said to be inconstant. It supplies the anterosuperior portion of the thalamus (fig 1 *E*).

Hillemand gave the following orientation concerning these five sources of blood supply in relation to the thalamus. A transverse section of the brain at the level of the mamillary bodies divides the thalamus into two blocks. In the anterior block the mesial portion is supplied by the premamillary branches and the lateral by the lenticulo-optic artery. In the posterior block the infero-internal portion is supplied by the thalamic perforating branches, the lateral inferior portion by the geniculate branches and the superior surface by the choroid branches.

When a horizontal section is cut through the central gray commissure which divides the thalamus into upper and lower portions, it is seen that the internal part of the superior block is supplied by the choroid artery and the external part by the lenticulo-optic artery. The internal part of the lower block is supplied by thalamoperforating branches and the external part by the geniculate branches.

Finally, when a sagittal section of the thalamus is made through the optic geniculate body, the anterior portion of the medial section is seen to be supplied by premamillary branches, the major part by thalamoperforating arteries and a small upper portion by the choroid branches. In the case of the outer block the anterior portion is supplied by the lenticulo-optic branches, an intermediate area by the thalamic perforating branches and the posterior area by the geniculate arteries.

The different nuclei of the thalamus may be considered separately in regard to their blood supply. The external nucleus is supplied in its posterior part by the geniculate artery. This usually includes the central medial nucleus of Luys and the semilunar nucleus of Flechsig. The lenticulo-optic branch supplies the anterior portion of the external nucleus, and the thalamic perforating arteries go to an intermediate portion. The anterior nucleus is in the territory of the lenticulo-optic artery. The pulvinar receives most of its blood supply from the choroid arteries, except for the antero-inferior portion, which is supplied by the geniculate arteries. The medial nucleus receives blood from the premamillary and postmamillary branches. The habenula lies within the choroid supply.

Although there are five sources of blood supply to the thalamus, the symptoms of occlusion of only two of these five sets of arteries are at present recognized. Thus, there are the syndrome of the geniculate arteries, or the true thalamic syndrome and the syndrome of the retromamillary or thalamoperforating branches. There may be combinations of the two. Added lesions of other branches of the posterior cerebral artery may give rise to associated symptoms, such as hemianopia or alexia.

With occlusion of the geniculate arteries producing the thalamic syndrome, the position of the lesion is always the same, although its extent is variable, giving rise to marked differences in the picture. The amount of the objective sensory changes and the degree of pain are in inverse proportion to each other. The pain is marked when the objective changes are slight and vice versa. The degree of objective sensory change depends on the degree of involvement of the central nucleus of Luys and nucleus semilunaris of Flechsig, where the sensory projection fibers end. The ataxia is dependent on the loss of deep sensation and also on destruction of the cerebellar fibers to the thalamus. The choreo-athetoid movements and voluntary contracture are related to the same factors. Hillemand related the vasomotor changes to injury of autonomic centers lying below the thalamus. He postulated that occlusion of the premamillary branches supplying the anterior nucleus of the thalamus would give rise to marked autonomic disturbances.

The second thalamic syndrome is dependent on involvement of the retromamillary branches, including the peduncular and thalamoperforating arteries. The predominant symptoms are incoordination and intention tremor. The red nucleus may be primarily involved or only the cerebellar fibers destined for the thalamus. Choreo-athetoid movements and sensory changes are inconstant. The anesthesia is dependent on involvement of the sensory pathway to the thalamus.

While a large part of the subthalamic region is supplied by perforating branches from the posterior cerebral artery, it must be realized that the lateral portion is supplied by the anterior choroid artery. There is some overlap of these two sources of blood. The subthalamic nucleus is usually supplied by branches both from the posterior cerebral and from the anterior choroid artery.

The French authors give little information concerning the mid-brain syndromes produced by occlusion of the branches of the posterior cerebral artery. They divide them into the syndrome of the lower portion of the red nucleus and that of the upper portion of the red nucleus. The syndrome of the lower portion includes paralysis

of the oculomotor innervation in whole or in part. In both types there are signs of cerebellar ataxia.

In most cases the lesion in the thalamus is of the nature of encephalomalacia related to thrombosis of the geniculate arteries. Certain authors have reported tumors in the thalamus which gave rise to the syndrome. Baudouin, Lhermitte and Lereboullet⁹ (1930) said they felt that hemorrhage into the thalamus is more common than has generally been supposed. There are certain clinical findings that tend to differentiate hemorrhage from thrombosis. Hemorrhage into the thalamus is likely to produce severe hemiplegia which regresses, leaving the sensory abnormalities predominant. When severe pain comes on at once after the vascular injury, hemorrhage has usually been the cause. The pain developing with encephalomalacia may not appear for weeks or months after the stroke. In many cases the hemorrhage breaks into the ventricular system, and blood appears in the spinal fluid. The bleeding is more widely destructive and is likely to produce a full blown thalamic syndrome.

In cases of the thalamic syndrome the pain is known as "central pain." It is dependent on an actual lesion of the central nervous system rather than any peripheral injury.

Roussy pointed out that there are two types of pain associated with hemiparesis. The first is pain of peripheral origin, which is found in cases of marked hemiplegia with contractures. Months or years after the onset, pain may occur in the extremities, especially around large joints. This pain is not continuous but tends to occur in crises produced by fatigue, traumatism or change in atmospheric conditions. It is of the nature of rheumatic pain. It is increased by movement, calmed by repose and helped by drugs. The central pain of the thalamic syndrome involves the whole side of the body. It has no exact localization. Sometimes it is largely superficial, at other times it is a deep pain. It is usually continuous but has exacerbations. Walking often makes the pain worse, so that the patient is incapacitated. It is also made worse when the skin is touched with the finger, by deep pressure and particularly by cold. It resembles in some ways a superficial or deep burn. Warmth is the only peripheral stimulus which may give a pleasant sensation. The pain may occur in the viscera, for example, in the bladder and rectum.

Head said he believed the central pain is due to the freeing of the thalamus from control of the cerebral cortex. There has been considerable discussion as to whether central pain can occur after injury of sensory pathways at lower levels than the thalamus.

⁹ Baudouin, A., Lhermitte, J., and Lereboullet, J. Une observation anatomo-clinique d'hémorragie du thalamus, *Rev. neurol.* 2: 102, 1930.

The thalamic syndrome is of extreme interest both from a physiologic and from a clinical point of view. Only in rare cases is the total picture present, but partial manifestations, particularly those of central pain, are observed in many patients with vascular lesions of the brain. This is related to the fact that so many arteries supply blood to the thalamic nuclei.

PULSATIONS OF THE WALL OF THE CHEST

I GENERAL CONSIDERATION

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The earlier clinicians, not having elaborate apparatus and complicated laboratory methods at their disposal, attempted to find signs of diagnostic value by careful observation at the bedside with the simplest clinical devices. Today these old clinical methods of examination cannot be renounced, indeed, special attention should be given to them. A large majority of physicians are not in a position to use elaborate apparatus or complicated laboratory methods at the bedside, furthermore, careful clinical observations—as may be demonstrated in the case of pulsatory phenomena—give important clues in diagnosis, clues such as can be brought to light by no other methods of examination, regardless of how elaborate. Following the example of the old clinicians, in my studies of diagnostically important pulsations of the wall of the chest I have made use of the simplest method, namely, careful inspection and palpation of the thoracic wall. In order that this method may lead to reliable results, it is indispensable that one learn it at the bedside and practice it intelligently.

METHOD

Palpation is done preferably with the hand slightly dorsiflexed, the base of the metacarpal bones being placed with slight pressure against the portion of the thoracic wall to be examined. A comparison with the radial pulse has proved to be advantageous in determining to which phase the pulsatory movement belongs. In comparison with the carotid pulse the radial pulse is delayed, but this is negligible in view of the fact that the pulsatory phenomena are of considerable duration, likewise, the carotid pulse is more easily accessible than the radial pulse. Determinations of the time made in this way have always been verified by graphic registrations. The correctness of the results acquired by inspection and palpation has been proved by a considerable number of postmortem examinations (25 per cent of all cases).¹ It can be shown that careful clinical observations, as previously indicated, are sufficient as a rule to determine the type of the pulsatory movement as well as the phase to which it belongs, provided there is no marked tachycardia. The graphic registration of movements of the thoracic

Translated by Hugo Roesler, M D, Philadelphia

From the *Herzstation*, Dr. Hans Horst Meyer and Dr. Emil Zak, directors

1 A total of twenty-five normal persons and one hundred and twenty-eight patients have been studied. The results of these studies are presented in my book entitled "Die Brustwandpulsationen als Symptome von Herz- und Gefasskrankheiten" (Vienna, Wilhelm Maudrich, 1933)

wall has been used mainly for control purposes and in order to demonstrate objectively the findings obtained on palpation

The receptor for registration of the movements of the thoracic wall should not be attached directly to the wall, since this would permit only the registration of the displacement of soft tissue. Pulsatory phenomena, however, are mostly represented clinically by diffuse movements affecting ribs and soft tissues equally. The receiver, which is to be placed on the thoracic wall, must be held in position by a stationary support which is fastened preferably to the bed. The receptor (fig 1) consists of a shallow metal disk-shaped chamber (*D*), measuring 5.5 cm in diameter and 1 cm in height, over which is stretched a rubber membrane (*M*), which should not be too thin. To this membrane is attached a cork plate (*K*) which is large enough to cover one intercostal space and both adjacent

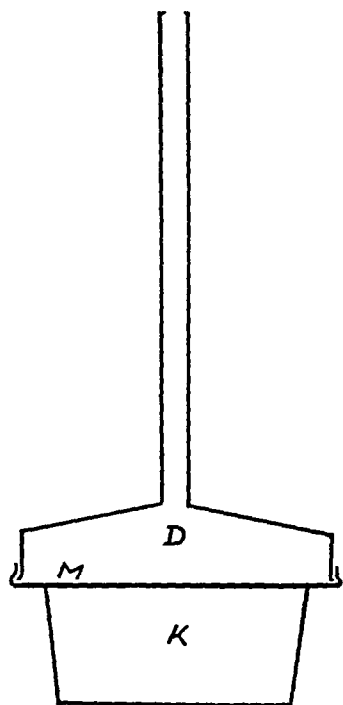


Fig 1—Receptor for registering the movements of the thoracic wall. *D* is the metal receiver, *M*, the rubber membrane, and *K*, the cork plate.

ribs. This cork plate rests on the portion of the wall to be examined and transmits the thoracic movements to the rubber membrane and by air transmission on a Marey tambour to a Jacquet polygraph.

PRELIMINARY PHYSIOLOGIC CONSIDERATIONS

It is necessary to recall some of the physiologic movements of the heart in order to understand pulsatory movements of the thoracic wall.

The heart undergoes a change in consistency during systole—it becomes hard and tense. In addition, its curvature is increased, as was shown by the physiologist Ludwig, by an increase in the anteroposterior and a decrease in the transverse diameters (fig 2). The most important

and powerful movement which the heart makes during systole, is however, lever-like, it revolves on its transverse axis so that the apical portion is raised and pushes against the anterior wall of the chest. This movement is of decided importance in the formation of the apical thrust. Simultaneously with the changes in shape, the volume of the heart diminishes. This involves two processes: (1) a longitudinal shortening of the ventricular cone whereby the auriculoventricular septum moves toward the apex, (2) a centripetal marginal change, which may be distinctly recognized roentgenologically as a pulsating movement, particularly of the left margin of the heart. The latter movement is of comparatively little significance in the systolic diminution of the size of the heart. The longitudinal shortening of the ventricular cone plays the most important rôle.

The systolic change in shape of the heart and the diminution in volume are primarily responsible for the pulsations of the thoracic wall. One must not forget that these two processes have simultaneously opposing effects on the thoracic wall. The change in shape, i. e., the

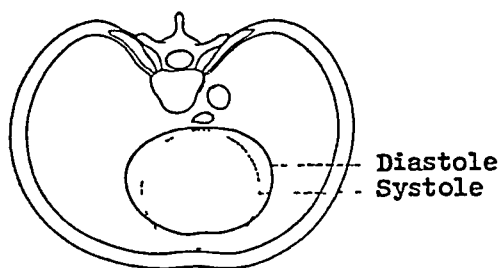


Fig 2—Cross-section through the heart and chest. The dash line indicates the changes in the heart during systole.

increase in curvature and particularly the rise of the apical portion during systole, causes a centrifugal movement and forces the thoracic wall outward, whereas the diminution in volume tends to draw it inward. The simultaneous effect of these two opposing forces, which may reveal differences under pathologic conditions, produces a number of pulsatory phenomena the analysis of which presents considerable difficulty. Thus, pulsatory movements which have been thoroughly investigated, such as the apical thrust, will be passed over, and only those few will be dealt with which claim special attention and interest from a diagnostic point of view. Some of them are not even mentioned in textbooks, and as to the origin of others there exist rather erroneous concepts.

SYSTOLIC PULSATION IN THE REGION OF THE RIGHT VENTRICLE

Under normal conditions the thoracic wall in the region of the right ventricle, i. e., the lower third of the sternum and the fourth and fifth intercostal spaces as far as the left parasternal line, usually shows no pulsation, for the two opposing systolic forces equalize each other. Not

uncommonly, particularly in a young person with an elastic thoracic wall, a slight systolic depression may be seen in the region of the right ventricle when the aspiratory force of systole (reduction of ventricular volume during systolic efflux) predominates Mackenzie,² who found this depression in his graphs of the pulsations of the thoracic wall, concluded erroneously that the systole of the pathologically enlarged right ventricle always induces a depression of the thoracic wall, and this opinion is still included frequently in textbooks. The exact opposite is correct, as can easily be seen in instances of mitral stenosis. The enlargement of the right ventricle is primarily laterad, since the inflexible thoracic wall in front and the firm dorsal portion of the pericardium offer considerable resistance to dilatation in an anteroposterior direction. Hence, the heart is flattened, the base taking the form of a transverse ellipse. During systole the elliptic cross-section of the heart becomes more spherical, as shown by Ludwig, and the anteroposterior diameter increases (fig 2). The result is a large systolic bulging of the anterior portion of the wall of the chest in the region of the right ventricle, this is palpable and often visible. This sign is predominantly found in patients with advanced mitral stenosis. Aside from hypertrophy and dilatation of the right ventricle, the dilatation of the left auricle is of importance, for it presses the heart against the anterior portion of the thoracic wall and thus furthers the development of the systolic bulging.

A. G. was a man aged 32. The postmortem diagnosis was mitral regurgitation and stenosis, with hypertrophy and dilatation of both ventricles and auricles. Clinically there was diffuse bulging in the cardiac area. The apical thrust was considerably widened, heaving and resistant, reaching to the anterior axillary line in the sixth intercostal space. The whole precordial area was lifted during systole (fig 3), and this was more marked from the fourth to the sixth intercostal space between the sternum and the left parasternal line. The systolic bulge extended caudad to the costal arch at the left of the nipple line. At the right it reached 1 inch (2.5 cm) beyond the right sternal border. Percussion revealed absolute flatness over the lower sternal portion caudad from the fourth rib. The cardiac dullness extended in the fifth intercostal space 2 inches (5 cm) beyond the right sternal border. To the left of the sternum and in the left intercostal space there was an area of flatness 3 inches (7.5 cm) in width. Auscultation revealed over the apical area a long, loud systolic and a short, rough diastolic murmur. At the base over the aorta there was a weak first sound, scarcely audible. There were similar auscultatory findings over the pulmonary artery; in addition, the pulmonic second sound was fairly loud. Roentgenograms showed a large silhouette of mitral configuration, with marked enlargement of the left auricle, which when projected on the anterior wall of the chest extended from the fourth rib to the xiphoid process.

2 Mackenzie, J. *Lehrbuch der Herzkrankheiten*, German translation by C. J. Rothberger, Berlin, Julius Springer, 1923.

The systolic lift of the precordial area should be regarded as a prognostically unfavorable sign, for it is never demonstrated in the presence of mitral stenosis of slight degree. The appearance of this sign requires the presence of considerable enlargement of the right ventricle, indicating a valvular defect of higher degree and inadequate compensation. Clinically demonstrable dilatations are usually to be regarded as myogenic, i. e., distentions due to muscular failure (Romberg³)

SYSTOLIC DEPRESSIONS OF THE THORACIC WALL

The systolic depressions of the thoracic wall are of importance in the diagnosis of certain diseases of the heart provided they are diffuse, spreading over several intercostal spaces, and affect both ribs and soft tissues

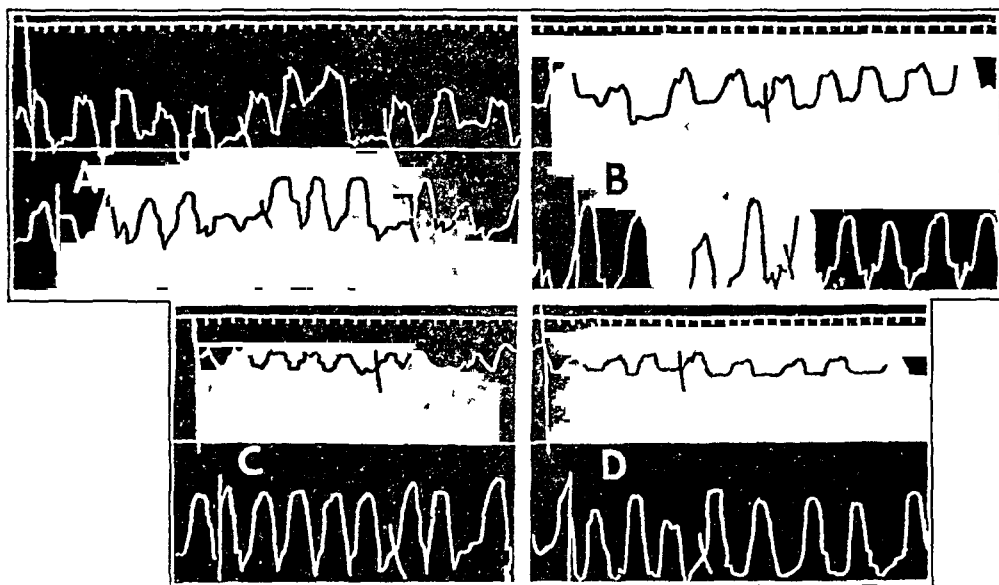


Fig 3—Graphs illustrating the pulsatory propulsion of the cardiac area in the presence of a high grade lesion of the mitral valve (proved at postmortem examination). The lower graph represents the apical thrust. The upper graph shows the propulsion at A, the left parasternal line at the fourth intercostal space, B, the lower sternal area, C, the right parasternal line at the fourth intercostal space, and D, the sternum at the level of the second rib.

The centripetal forces due to diminution in cardiac volume are of paramount importance for the development of systolic depressions of the thoracic wall. In raising the question as to how the centripetal forces produce these depressions, one stumbles again and again on the erroneous concept that pericardial adhesions are an indispensable prerequisite, and yet it is a fact that these depressions are encountered

3 Romberg, E. *Lehrbuch der Krankheiten des Herzens und der Blutgefäße*, ed 4, Stuttgart, F. Enke, 1925.

far more frequently in the absence than in the presence of pericardial adhesions. The fact should not be lost sight of that a systolic diminution in volume, independent of adhesions, affects the thoracic wall in two ways. First, it exerts a *direct* aspiratory effect on the wall as far as the heart touches it, second, it acts *indirectly* as suction independent of the contact of the heart with the thoracic wall, because of the fall in intrathoracic pressure due to the rapid outflow of blood from the thoracic cavity during systole.

The direct aspiratory effect of the systolic diminution in volume is seen only when the thoracic wall and the heart are in contact. According to laws of physics, that portion of the thoracic wall must follow the centripetal movement of the heart (Kiwisch⁴) even when no adhesions are present, provided no other tissue, i. e., the lung, quickly takes up this space left vacant between the heart and the thoracic wall. A systolic depression of the wall results, especially when the lungs cannot fulfil this function of buffer, from adhesions between the heart and the thoracic wall, with obliteration of the costomediastinal pleural sinus, or from compression of the bordering portion of the lungs by an equally enlarged heart. More than anything else, however, an increase in the marginal excursions of the ventricle exerts an aspiratory effect on the thoracic wall, whether the stroke volume is increased or the mechanism of systole is altered, in that the marginal movements predominate over the longitudinal shortening of the ventricular cone. A second more or less important factor in the formation of the depression is the *indirect* aspiratory action of the systolic diminution in volume, this has been pointed out by Mackenzie² and Lang⁵. It is due to the decrease in the intrathoracic pressure occurring during systole, when the blood flows out of the thoracic cavity. Hence a slight depression of the thoracic wall may occasionally be seen even in a healthy person. The aspiratory action on the thoracic wall is especially pronounced in certain pathologic conditions, for instance, when the stroke volume of one ventricle and the volume of blood flowing out of the thoracic cavity are increased, as is the case in tricuspid and aortic regurgitation. The abruptness of the decrease in intrathoracic pressure during systole also is important. The more rapid the outflow of blood from the thoracic cavity, the less able will the inflow of venous blood and air—the compensating factors—be to keep pace with and counteract the considerable fall in systolic intrathoracic pressure.

4 Kiwisch von Rotterau, F. Neue Theorie des Herzstosses, Vrtljschr f d prakt Heilk 9 143, 1846

5 Lang, G. Ueber einige durch die Herzaktion verursachte Bewegungen der Brustwand und des Epigastriums, Deutsches Arch f klin Med 108 35, 1912

Finally it is important to know that the effect of systolic aspiration on the thoracic wall is compensated for not only by the factors just mentioned (aspiration of arterial and venous blood) but also by the centrifugal force of the systolic change in shape.

In summarizing, it may be said that pathologic depressions of the anterior wall of the chest are produced by three conditions: (1) increased systolic aspiration (increased aspiratory effects due to systolic diminution in cardiac volume), (2) interference with the function of the pulmonary cushion and (3) inhibition of the systolic change in shape of the heart. Often several of these factors combine to present a distinct and diffuse depression of the thoracic wall. This type of pulsation is noted in three diseases: adhesive pericarditis, tricuspid regurgitation and aortic regurgitation.

The depression of the thoracic wall which is caused by systolic aspiration has been rightly designated by Weltmann⁶ as systolic depression, for in most cases these depressions of the thoracic wall are due not to an inward pull by pericardial adhesions but to the inward pressure of the wall caused by the outer atmospheric pressure, which is merely a sequela of systolic aspiration. The anterior portion of the wall is particularly affected, because it is next to the heart and more flexible than the posterior portions, which are fixed by the spine.

The effect of the direct aspiration does not extend beyond the precordial area and is more marked as a rule in the left midclavicular line, while it is scarcely perceptible in the sternal area. The effect of the indirect aspiration, however, extends beyond the cardiac area, particularly with the marked decrease of the intrathoracic pressure, and it may in exceptional cases include the dorsal portions of the left side, resulting in a depression described as Broadbent's sign.

PULSATIONS OF THE WALL OF THE CHEST CAUSED BY THE LIVER

Between the sixth rib and the costal arch the liver is in contact with the anterior wall of the chest, separated from it only by the diaphragm and the costophrenic sinus, thus it may transmit its pulsatory movements to the thoracic wall. It is an error to believe that under normal conditions the liver reveals no pulsations, even such an excellent observer as Vaquez⁷ stated in his textbook that pulsatory movements can be found only when there is congestion of the liver in connection with cardiac failure. Graphic registration of the hepatic pulse in normal persons has shown that this concept is not correct.

⁶ Weltmann, O. Ueber sichtbare Pulsationsphänomene in der Herzgegend, *Wien klin Wchnschr* 42: 829 (June 20) 1929.

⁷ Vaquez, H. *Diseases of the Heart*, translated by G. F. Laidlaw, Philadelphia, W. B. Saunders Company, 1924.

Von Kapff⁸ obtained for healthy persons by means of a mirror sphygmograph a hepatogram showing the characteristics of a normal auricular venous pulse consisting of an auricular and a ventricular wave, with a typical systolic depression in between.

Three factors account for the hepatic pulse (1) the movement of the column of venous blood explained by an increase and a decrease in the size of the organ, corresponding to the respective phases of the cardiac cycle, (2) the transmission of movements of the heart from its diaphragmatic aspect through the diaphragm to the surface of the left lobe of the liver and (3) the systolic aspiration, not only influencing the column of venous blood but causing a direct aspiratory effect on the diaphragmatic surface of the liver. The last two factors, cardiac movement and systolic aspiration, act similarly on the liver, by causing a cephalad displacement of the whole organ during systole.

In discussing hepatic pulsations one should distinguish between volumetric variations, caused primarily by the afflux and efflux of venous blood and movements of the whole organ. Mackenzie has expressed the opinion that only the latter condition, i. e., a systolic upward shift of the liver, is observed under physiologic conditions, while a venous hepatic pulse is noted exclusively under pathologic conditions. Von Kapff, obviously influenced by Mackenzie's opinion, likewise has stated that the marked systolic depression which he found in his hepatograms is influenced by the upward shift of the liver rather than by the efflux of venous blood. The following personal observations disprove such an interpretation of the phenomena of systolic pulsation. If one places the hand over the right costal arch of a healthy person, particularly an adolescent child one perceives the cephalad movement of the palpating hand which corresponds to a systolic depression of the caudal surface of the liver, but one notices a similar phenomenon when the hand is placed with slight pressure in front of the right wall of the chest, over the hepatic area. One then perceives definitely a systolic depression of the thoracic wall over this area. This finding cannot be explained by assuming that the liver moves cephalad during systole, both phenomena are easily interpreted by assuming that the liver diminishes in size during systole because of aspiration of venous blood into the chest.

The correctness of this concept is proved by Hitzenger's⁹ roentgenologic observations of the pulsating diaphragm. A systolic upward movement of the diaphragm was observed only along the left leaf, where the thin left lobe of the liver is almost in the direct vicinity of the heart. Here the diaphragm is influenced by the systolic aspiratory

8 von Kapff, W. Ueber die Leberpulsation. I. Der normale Leberpuls, *Deutsches Arch. f. klin. Med.* **149**: 279, 1925.

9 Hitzenger, K. Das Zwerchfell im gesunden und kranken Zustand, Berlin, Julius Springer, 1927.

effect The right leaf of the diaphragm, however, particularly in its lateral portion, showed an entirely different type of pulsation There was a slow presystolic cephalad movement which was followed by a rapid and marked systolic amplitude in a caudal direction The systolic movement of the diaphragm, therefore, takes place in a direction opposite to what one would expect from an upward shift of the whole liver Indeed, Hitzzenberger, has said he considers the systolic pulsations of the right diaphragmatic leaf as an expression of a direct venous hepatic pulse There is no doubt, therefore, that the systolic depression of the ventral wall of the chest over the hepatic area, as well as the depression in the hepatogram, is caused by the systolic efflux of venous blood from the liver The degree of pulsatory amplitudes of the thoracic wall over the hepatic area is small under normal conditions This movement is best perceived when the subject is holding his breath The palm of the examiner's right hand is placed with moderate pressure on the right wall of the chest near the costal arch and approximately in the nipple line, while the left hand palpates the pulse in the radial artery A jerky systolic depression is noted which may be found as high as the level of the fifth rib, but it increases in intensity caudad toward the costal arch Similarly, there is found a systolic depression of the abdominal wall in the epigastric area This pulsation in the hepatic area is hardly ever missed in an adolescent child, because the chest is elastic and flexible, it is noted in different degrees in different persons

The degree of the systolic depression in the hepatogram as well as the degree of the palpable depression over the hepatic area, depends on two factors (1) the diastolic and particularly the presystolic active emptying of the right auricle, which is the prerequisite for a powerful systolic influx of blood from the liver, and (2) the force of ventricular contraction, which in two ways fosters the systolic influx of venous blood into the chest First, the pulling down of the auriculoventricular septum suddenly increases the volume of the auricle, and, second, the diminution of the volume of the ventricle (the efflux of blood from the thoracic cavity) leads to a fall in pressure These factors act in the same way on the venous blood, causing powerful aspiration

Under abnormal conditions these factors change, and certain anomalies are found in the hepatograms as well as in the pulsatory phenomena of the thoracic wall The systolic depression of the venous pulse is more marked when the stroke volume of the ventricle increases, causing a greater amount of blood to leave the thoracic cavity Von Kapff found a particularly marked descent in the hepatograms of patients with aortic regurgitation In patients with the same valvular lesion I have found not uncommonly a particularly marked systolic depression of the thoracic wall over the hepatic area (fig 4A)

Failure of the right ventricle with associated overdilatation of the right auricle and venous congestion, of course, will counteract the formation of a typical depression in the venous pulse and occasionally may even cause a reversal of the venous pulse picture. Similar changes are observed with the appearance of auricular fibrillation, here the pre-systolic emptying of the auricle does not take place, and with it the most important prerequisite for the systolic afflux of venous blood disappears, particularly in the presence of failure of the right side of the heart. Hence, the influx of blood into the right auricle takes place almost exclusively during diastole and not, as under normal conditions, predominantly during systole, with marked congestion blood flows into the right auricle only at the beginning of diastole, i. e., when the relaxed

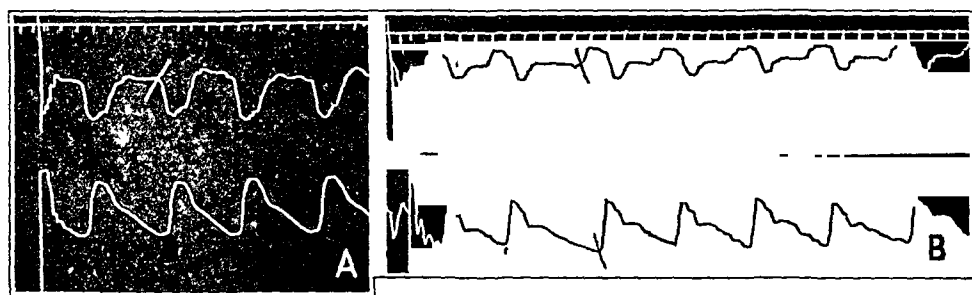


Fig 4—*A*, a graph of the systolic depression of the hepatic area observed in a case of aortic regurgitation of syphilitic etiology. The lower graph is for the radial artery. The upper graph was made with the receiver over the seventh and eighth ribs on the right side, 2 cm within the anterior axillary line. The mark indicates the beginning of expulsion. *B*, a graph of the pulsatory propulsion of the hepatic area in a case of tricuspid regurgitation. The lower graph is for the radial artery. The upper graph was made with the receiver over the seventh rib in the midaxillary line on the right side.

right ventricle, after opening of the auriculoventricular valves, offers space for the venous influx. Then a ventricular hepatic pulse results with a systolic level and a more or less steep descent at the beginning of diastole.

With this type of venous hepatic pulse, the systolic ascent is caused by congestion only, and this ascent is less easily palpable than the steep diastolic descent (diastolic collapse of the liver). The findings on palpation are again different for that type of ventricular hepatic pulse which is due to regurgitation of blood from the right ventricle in the presence of tricuspid regurgitation. Its graph differs little from the graph of the pulsation due to congestion, but palpation does not demonstrate the diastolic collapse of the liver as much as the forceful systolic elevation caused by the impact of the regurgitating blood. Not only does the bulge affect the caudal portions of the right wall of the chest in a ventral direction but commonly a definite shift from left to

right is noted (fig 4*B*) This is due to the fact that the right lobe of the liver is much larger than the left lobe, so that the larger amount of the regurgitating blood flows to the right side This results in a strong impulse to the liver, which not rarely leads to a systolic shift of the whole chest, particularly the lower portions, from left to right This finding may be so obvious that the diagnosis of tricuspid regurgitation may be made by merely inspecting the chest

It is not possible under normal conditions to palpate elevations of the thoracic wall which would correspond to the auricular (or ventricular) wave of the hepatogram, the force of these venous pulsations, caused merely by stasis, is too small as a rule to produce a palpable change in the surface of the liver If, however, there is an impediment to the flow of venous blood into the ventricle during auricular contraction, a presystolic lift can be palpated in the hepatic area This is found when there is congestion in the right side of the heart particularly in the presence of tricuspid stenosis, in which the right auricle partly throws blood back into the veins, provided it is still capable of contraction Thus, a presystolic regurgitation pulse results, which, as compared with the pulse accompanying stasis, may be felt as a slight elevation on the surface of the liver as well as occasionally on the wall of the chest as far as it covers the liver (fig 5), the elevation definitely precedes the radial pulse With associated tricuspid regurgitation there is added to the presystolic regurgitation a wave of systolic regurgitation, and a double wave in the hepatic pulse results, sometimes the first (auricular) and sometimes the second (ventricular) elevation is more marked

ASSOCIATED PULSATORY MOVEMENTS (SECONDARY PULSATIONS), PULSATIONS OF THE CHEST IN THE FRONTAL DIRECTION

It will be necessary for the understanding of the sometimes rather complicated pulsatory phenomena to consider certain pulsatory movements which are a distinct effect of those primary movements of the thoracic wall which originate at the place of the immediate, direct effect of pulsation The chest represents a stiff elastic system If a pulsatory force sets up a deformation in one area, movements will not be limited to this circumscribed part but will take place also at some distance from it Such movements may be designated as secondary pulsations or associated pulsatory movements

The type and degree of these associated pulsatory movements are influenced by several factors the force of the primary pulsatory impact, the point and direction of impact and the elasticity and flexibility of the bony thoracic wall Needless to say the associated movements take place in the immediate vicinity of the pulsatory impact, and they

have the same direction as have the primary pulsations. Much more important are those distant effects of pulsatory force which, in a certain sense, take place opposite to the main pulsations. A pulsatory bulge of the thoracic wall leads to a distant flattening or depression of the ribs, and vice versa. As an example of the distant effect of the primary pulsations, one may cite the flattening of the lateral portions of the ribs in association with a powerful propulsion of the midportion of the thoracic wall, as observed in hypertrophy and dilatation of the right ventricle (fig 6*A*). In the presence of mitral lesions one frequently observes a definite inward systolic pulsatory movement of the lateral portion of the chest extending from the fifth to the eighth rib and occasionally down to the costal arch. This associated pulsatory movement is usually much more pronounced on the right side. The following explanation may be offered. The primary pulsatory propulsion of the midportion of the thoracic wall extends rather far to the left, because



Fig 5—*A*, a graph showing the presystolic propulsion of the hepatic area in a case of tricuspid stenosis, compared with, *B*, a graph demonstrating the pulse in the jugular vein. The lower graph in *A* shows the apical thrust. The upper graph was made with the receiver over the right costal arch in the midclavicular line. The mark corresponds to the ascent of the apical thrust. The steep ascent in the upper graph precedes the beginning of the apical thrust (presystolic-auricular wave). The upper graph in *B* shows movement of the liver as in *A*. The lower graph is for the pulsation of the jugular vein. The graphs resemble each other.

of the asymmetrical portion of the right ventricle, this counteracts to a certain degree the formation of an oppositely directed movement on the left side.

If a pulsatory force acts on one side of the chest, an associated movement of the symmetrical portion of the other side is called forth, and thus, in connection with the primary pulsation, leads as a rule to a shift of the whole chest in a predominantly frontal direction. Thus a strong impulse directed at the left side to the left and ventrad, as caused by the impact of a hypertrophic left ventricle, is associated on the right side with a flattening out of the ribs, i. e., a movement to the left and dorsad (fig 6*B*). The total pulsatory effect will be a shift of the

whole chest in a frontal direction from right to left and more marked in the more flexible caudal portions of the chest. Thus one notices occasionally in the presence of aortic regurgitation or hypertensive disease a jerky, easily visible shift to the left, expressing the increased activity of the left ventricle. As compared with the predominant frontal direction of the movement, the sagittal (dorsoventral and ventrodorsal) component is less conspicuous, but on careful observation one may notice that simultaneous with the shift of the chest to the left a kind of rotation around the long axis takes place, so that the ribs on the left side protrude while those on the right undergo depression, i. e., they move dorsad. The frontal movement from right to left (systole) is best marked in the portions adjacent to the sternum particularly over the sternum itself.

It is easily understood that a primary propulsion on the right side leads to a shift of the whole chest from left to right. Such pulsations are sometimes noted in cases of aneurysmal enlargement of the left

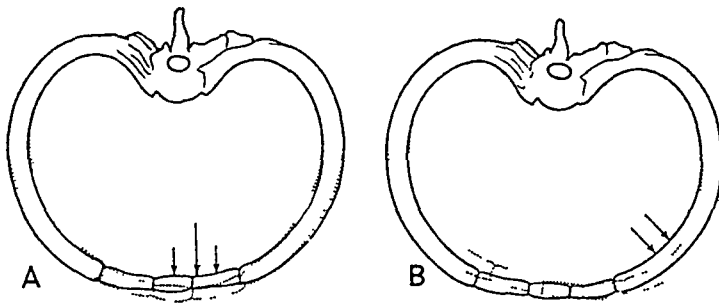


Fig. 6—The dotted lines indicate the pulsatory shift of the thoracic wall, *A*, for a patient with a valvular lesion and hypertrophy of the right ventricle, *B*, for a patient with hypertension or a lesion of the aortic valve. The arrows indicate the direction of the primary force.

auricle, when in the presence of high grade mitral regurgitation the impact of the blood stream hits the right side of the chest. Moreover, in cases of tricuspid regurgitation the venous pulse of the liver is transmitted to the adjacent portions of the right side of the chest.

An opposite type of movement along the symmetrical portions of the contralateral part of the chest will be observed if the primary pulsatory force is not directed outward but inward, or, to express it differently, if a primary depression of the ribs takes place over half the chest. Here one will observe a propulsion of the ribs. Of this one may convince oneself by the following simple experiment. If slight pressure with the tips of the fingers is exerted against the bony thoracic wall in the region of the apical thrust, one notices simultaneously at the right side a slight propulsion and shift of the thoracic wall to the right. This roughly corresponds to those pulsations which may be observed in the patient with an adherent pericardium with systolic

depression of the cardiac area. Simultaneously with the depression of the ribs, a shift to the right is noted and the compensation, with the movement to the right of the right half of the chest, again results in a frontal type of pulsation. This movement is hardly ever as marked as the frontal shift of the thorax in the opposite direction, as noted with increased activity of the left ventricle, this is explained by the lesser intensity of the primary force in the presence of an adherent pericardium. When the latter condition is present the systolic shift of the chest from left to right is not as marked as the jerky rebound of the thoracic wall noted during diastole.

SUMMARY

Examination by means of simple inspection and palpation is almost always sufficient to demonstrate diagnostically important pulsatory findings. The graphic registration serves merely to control the clinical findings, it should be carried out with the fixed receptor.

Pulsatory movements of the thoracic wall are essentially caused by the effect of change in shape and diminution in volume of the heart. Hypertrophy and dilatation of the right chamber in association with the dilatation of the left auricle, as encountered in cases of lesions of the mitral valve of a severe degree, lead to a forceful systolic propulsion of the precordial area near the sternum.

Systolic depressions of the thoracic wall are due to the centripetally directed movement of the cardiac systole, which exerts an aspiratory effect on the thoracic wall in two ways: (1) directly, when the heart is in contact with the thoracic wall, and (2) indirectly, owing to the fall in intrathoracic pressure caused by systole. The effect of these aspiratory forces on the thoracic wall is equalized under normal conditions mainly by two factors: (1) the oppositely directed propulsive force due to the systolic change in shape of the heart and (2) the expansion of the lungs.

Pathologic depressions of the thoracic wall during systole are due to (1) marked increase of the systolic aspiratory effect (reduction of ventricular volume during the systolic efflux), (2) inhibition of the systolic change in shape of the heart and (3) inhibition of the expansion of the lungs.

An increase of the stroke volume much more commonly causes systolic depression of the thoracic wall than do adhesions of the pericardium.

The liver may transmit its pulsatory movements to the adjacent thoracic wall. Normally the systolic efflux of venous blood from the liver often causes a depression of the portions of the thoracic wall in front of it. The systolic depression is often particularly marked in the

presence of aortic regurgitation, this is due to the increase in stroke volume and the increased aspiratory effect. Tricuspid regurgitation as a rule causes a forceful systolic propulsion of the hepatic area. The systolic impulse of the blood regurgitating into the large right lobe of the liver transmits to the whole chest a frontal movement directed from left to right. A presystolic propulsion of the thoracic wall over the hepatic area is often noted in congestive failure of the right side of the heart but particularly in the presence of tricuspid stenosis, provided the auricle is still capable of contraction.

In addition to primary pulsatory phenomena, which occur directly at the place of the pulsatory impact, secondary pulsations or associated pulsatory movements are observed. They should be looked on as distinct effects of the primary pulsatory forces. Pulsatory movements of the whole chest in a frontal direction are caused by a compensatory effect of both types of pulsations, this is observed when there is marked hypertrophy of the left ventricle, tricuspid regurgitation or mitral regurgitation, associated with aneurysmal dilatation of the left auricle to the right.

PRESENCE OF DIGITALIS IN BODY FLUIDS OF DIGITALIZED PATIENTS

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During the treatment of patients with congestive heart failure we have occasionally observed that from twenty-four to forty-eight hours after diuresis has been produced by the use of salyrgan or mercurin (the sodium salt of trimethylcyclopentane-dicarboxylic acid-methoxy-mercuryhydroxideallylamide) or with theophylline the patient has become ill, with nausea vomiting, giddiness, headache and considerable weakness. In fact in the past several years one of us has seen two patients, not alarmingly ill before such supplemental diuresis, come to rapid unexpected death in this sickness a day or two after salyrgan had been given. It is this occasional postdiuretic illness that initiated the present investigation.

There are several hypotheses that may be offered as an explanation of the symptoms that may follow diuresis induced with salyrgan. When given in the usual doses, of 1 or 2 cc, this drug may produce no diuresis, in which case the mercury may be retained in the body and cause untoward effects. However, it is not with that circumstance that we are concerned, because the illness which we are considering occurred after an output of from 2,000 to 6,000 cc of fluid. With the elimination of such quantities of fluid, Keith and Whelan¹ have shown that 85 per cent of the mercury injected is excreted and can be recovered in the subsequent twenty-four hour specimen of urine in most instances. That, together with the common observation that repeated injections of salyrgan cause no appreciable renal damage, makes it seem unlikely that the mercury alone is the direct cause of the postdiuretic symptoms.

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¹ Keith, N. M., and Whelan, M. A Study of the Action of Ammonium Chloride and Organic Mercury Compounds, *J. Clin. Investigation* 3: 149, 1926

A shift in the electrolytes of the body may be the explanation for such symptoms.² It has been found³ that organic mercury compounds when used alone cause an increased excretion of chloride and inorganic fixed base in the urine. If the diuresis is great, there is a concomitant decrease in the chloride and an increase in the bicarbonate concentration of the serum. Blumgart, Gilligan and Volk^{3a} found that alterations in the chloride and the bicarbonate content in human beings were opposite but about equal and greatest in the cases in which diuresis was the most marked. If a change in the electrolytes of the serum were to explain the symptoms, one might expect that the patient having a urinary output of 6 000 cc or more after the administration of salyrgan would be the one to experience the ill effects. But it has been our observation that the excretion of a large quantity of fluid is not necessarily the important factor. Moreover, the studies that have been referred to showed no substantial change in the acid-base equilibrium in the blood or urine under such circumstances. Furthermore, the changes in the specific gravity of the serum and in the protein content of the blood are not constant or marked, even when the diuresis is great. Furthermore, since the publication of Keith and Whelan's studies, ammonium chloride or a similar acid-producing salt is usually given in preparation before the use of salyrgan. As pointed out by Blumgart and his co-workers, the administration of an acid-producing salt tends to obviate any great alteration in electrolytes and in the chloride and the bicarbonate concentration of the serum. Since it is with this combination of ammonium chloride and salyrgan that we have usually observed these postdiuretic symptoms, we feel that a shift in electrolytes is probably not the explanation.

2 Since this was written an article entitled "Untoward Effects of Diuresis, with Special Reference to Mercurial Diuretics" by D. Poll and J. E. Stern has appeared (*Arch. Int. Med.* **58** 1087 [Dec.] 1936). They have attributed the syndrome primarily to depletion of water and chloride.

3 (a) Crawford, J. H., and McIntosh, J. P. Observations on the Use of Novasurol in Edema Due to Heart Failure, *J. Clin. Investigation* **1** 333, 1925. (b) Nothmann, M. Beobachtungen bei der Salyrgandiurese, *Ztschr. f. klin. Med.* **120** 158, 1932. (c) Fulton, M. N., Van Auken, H. A., Parsons, R. J., and Davenport, L. F. The Comparative Effect of Various Diuretics in Dogs with Special Reference to the Excretion of Urine, Chloride, and Urea, *J. Pharmacol. & Exper. Therap.* **50** 223, 1934. (d) Gilligan, D. R., Volk, M. C., and Blumgart, H. L. Observations on the Chemical and Physical Relation Between Blood Serum and Body Fluids. I. The Nature of Edema Fluids and Evidence Regarding the Mechanism of Edema Formation, *J. Clin. Investigation* **13** 365, 1934. (e) Blumgart, H. L., Gilligan, D. R., and Volk, M. C. Action of Diuretic Drugs. II. Effect of Diuretic Drugs on the Acid-Base Equilibrium of the Blood in Patients with Cardiac Edema, in *Medical Papers Dedicated to Henry Asbury Christian*, Baltimore, Waverly Press, Inc., 1936, p. 191. (f) Keith and Whelan.¹

An exchange of fluids in the body and relative dehydration of the tissues, occurring with marked diuresis, may be another factor in the production of such symptoms. One possibility in which this factor of relative dehydration of the tissues may play an important rôle is in the loss of fluid in and around the brain substance, causing a disturbance in the equilibrium of the dynamics of the blood and cerebrospinal fluid.

However, with the elimination of so much fluid from the body cavities and interstitial spaces through the blood stream and out through the kidneys, it seemed to us that a plausible explanation for such symptoms would be "digitalization." In other words, if substances which act like digitalis could be found in edema fluid from the pleurae, peritoneum and leg, the transportation of that fluid through the body to the kidneys during active diuresis in a patient who is digitalized would expose the cardiovascular and nervous systems to the contained digitalis and would cause further action of the drug. The symptoms experienced by these patients would then be those of digitalis intoxication. To all clinical appearances, too, the weakness, nausea, vomiting, headache and other symptoms seem to be similar to those due to an excess of digitalis. A similar idea has been put forward by Miller and Smith,⁴ but unfortunately their work has been reported only in abstract.

This hypothesis would be further validated if appreciable amounts of digitalis could be found in the body fluids of digitalized patients. Hatcher and Eggleston,⁵ Cloetta⁶ and Fischer⁷ have found small amounts of the principles of digitalis in the urine, although earlier workers⁸ had been unable to detect the excretion of these substances by the kidneys. This indicates that all digitalis is not firmly and irreversibly fixed in the body tissues.

4 Miller, G. H., and Smith, F. H. The Presence of Digitalis in Edema Fluid and Its Possible Clinical Significance, *J. Clin. Investigation* **10** 666, 1931.

5 Hatcher, R. A., and Eggleston, C. Studies in the Elimination of Certain of the Digitalis Bodies from the Animal Organism, *J. Pharmacol. & Exper. Therap.* **12** 405, 1919.

6 Cloetta, M. Die Darstellung und chemische Zusammensetzung der aktiven Substanzen aus den Digitalisblättern. Ihre pharmakologischen und therapeutischen Eigenschaften, *Arch. f. exper. Path. u. Pharmacol.* **112** 261, 1926.

7 Fischer, H. Ueber Aufnahme, Bindung und Abbau von Digitalisstoffen und den daraus sich ergebenden Beziehungen zu ihrer Wirkung am Herzen, *Arch. f. exper. Path. u. Pharmacol.* **130** 111, 1928.

8 Polailon and Carville. Etude physiologique sur les effets toxiques de l'inee, *Arch. de physiol. norm. et path.* **4** 523 and 680, 1871-1872. Hedbom, K. Beiträge zur Kenntnis der Wirkungen des Antiarins, *Arch. f. exper. Path. u. Pharmacol.* **45** 317, 1901. Lhotak von Lhota, C. Untersuchungen über das Verhalten der Digitalisstoffe im Körper, besonders bei der Angewohnung an Dieselben, *Arch. internat. de pharmacodyn. et de therap.* **22** 61, 1912.

METHOD

Since digitoxin is one of the most active of the digitalis glucosides and since its action and properties are better known than those of many of the other glucosides,⁹ we attempted its extraction (or possibly that of digitoxigenin) from the body fluids of digitalized patients. On the basis of the medicolegal method of Schmidt,¹⁰ modified in terms of the known physical properties of digitoxin recorded by Hatcher¹¹ and in the "Dispensatory of the United States,"¹² we worked out a satisfactory method of extraction. Five hundred cubic centimeters or more of edema fluid from the pleurae, peritoneum or leg is acidified with a 25 per cent solution of acetic acid to a p_H of 5.2 (alcoholic methyl red being used as an indicator), which is near the iso-electric point for the precipitation of protein. To this is added an equal volume of 95 per cent alcohol, and the mixture is heated to 50 C on a steam bath. This is filtered while hot, giving a clear to slightly yellow filtrate. This is placed in a large flask and concentrated to about 25 cc in a vacuum at 40 to 50 C.¹³ This concentrate, which is a thin gummy mass, is extracted with 150 cc of 95 per cent alcohol and evaporated to dryness on a water bath at a temperature not higher than 45 C. This residue is dissolved in 20 cc of 10 per cent alcohol, from 4 to 6 drops of a 35 per cent solution of ammonium hydroxide is then added to make the solution just alkaline to litmus. This is extracted three or four times with chloroform in a separatory funnel. The solution of chloroform is brought to dryness by the air bath,¹⁴ and to this residue is added 3 cc of chloroform and a mixture of 10 cc of ether with 70 cc of purified petroleum benzine in a flask. The flask is sealed with a rubber stopper and allowed to stand in the cold room for from twenty-four to forty-eight hours. The final product is a fine gray-white precipitate, which is removed by centrifugation. This is taken up in 1 or 2 cc of Clark's solution¹⁵ and used in the Straub preparation of the heart.

Early in the study it was learned that less than 500 cc of fluid concentrated for digitalis substances was not productive of satisfactory results. Consequently we usually used from 1,000 to 2,000 cc and in several instances as much as 5,000 cc of edema fluid from the pleurae, peritoneum or leg.¹⁶ After the precipitate was obtained by the chemical method outlined, it was suspended in from 2 to

9 Jacobs, W. A. The Chemistry of the Cardiac Glucosides, *Physiol. Rev.* **13** 222, 1933. Elderfield, R. C. The Chemistry of the Cardiac Glucosides, *Chem. Rev.* **17** 187, 1935.

10 Schmidt, E. A. *Ausführliches Lehrbuch der pharmazeutischen Chemie Organisches Chemie*, Braunschweig, F. Vieweg & Sohn, 1911, vol. 2, pt. 2, p. 1884.

11 Hatcher, R. A. Some Observations on the Pharmacology of a Digitalis Body, *J. A. M. A.* **75** 460 (Aug. 14) 1920.

12 Wood, G. B. The Dispensatory of the United States of America, ed. 21. Philadelphia, J. B. Lippincott Company, 1926, p. 410.

13 Because of foaming of the solution, we obtained more satisfactory results by placing the filtrate in a large evaporating dish, set into a warm room at 37 C with an electric fan blowing over it.

14 Logan, M. A. An Apparatus for the Evaporation of Liquids in a Test Tube, *J. Biol. Chem.* **86** 761, 1930.

15 Sollmann, T. Manual of Pharmacology, ed. 5, Philadelphia, W. B. Saunders Company, 1936, p. 786.

16 Dr. R. E. Glendy, of the Massachusetts General Hospital, furnished us with two specimens of edema fluid from the leg.

4 cc of Clark's solution¹⁵ From 0.5 to 1 cc of this was placed in a Straub preparation of the frog heart

In all, a total of twenty-nine specimens of fluid from twenty-four patients were examined, in eighteen of which it was known that the edema accumulated while the drug was being taken. The eighteen "digitalized fluids" were specimens of edema fluid—ten from the pleurae, seven from the peritoneum and one from the leg. Two specimens of fluid—one from the pleurae and one from the leg—were examined when it was questionable whether digitalis had been taken. The remaining nine specimens—five pleural and four peritoneal—were from patients with cirrhosis of the liver, tuberculosis, neoplasm and other disorders in which it was definitely known that no digitalis had been used. These "nondigitalized fluids" were used as controls.

Male frogs of the species *Rana pipiens*, weighing from 20 to 40 Gm., were used for the Straub preparations of the heart. In the course of the experiments we found to some extent, but not strikingly so, the daily variation of the action of digitalis in frogs in the winter and in the spring months that has been spoken of particularly by the German writers and also by Chapman and Morrell¹⁷ in their report on the standardization of digitalis in Canada. For the most part, the known tinctures of digitalis used as controls in our experiments from September

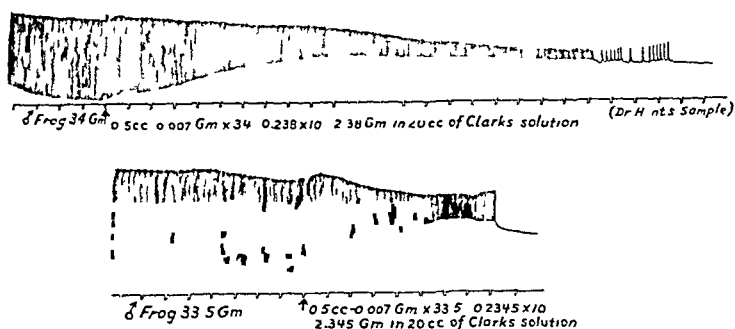


Chart 1—Two typical curves showing the digitalis effect in a Straub preparation of the heart, with systolic standstill. The dose was 0.007 Gm of digitalis per gram of body weight. The upstroke represents systole and the downstroke diastole.

1935 to April 1936 gave uniform results. Thus, we could conclude that the curves we obtained with our "digitalized fluids" were valid.

One of the first steps in this study was to determine whether or not the chemical procedure would recover digitalis added to body fluid. Several "nondigitalized fluids" were divided into two equal portions, to one portion from 2 to 3 cc of tincture of digitalis was added, while the other half was used as a control. In each of these trials the precipitate recovered from the fluid to which digitalis had been added, placed in a Straub preparation of the heart, showed a typical digitalis effect. No digitalis effect was obtained from the control half of the fluids.

RESULTS

Numerous experiments with the Straub preparation of the heart were performed from time to time with known strengths of fresh

17 Chapman, C. W., and Morrell, C. A. On the Biological Assay of Digitalis and Strophanthus, *J. Pharmacol. & Exper. Therap.* 46:229, 1932.

tincture of digitalis, supplied by Dr Reid Hunt. Various strengths were used, and chart 1 illustrates two typical curves obtained from the hearts of 33.5 and 34 Gm frogs with 0.007 Gm of digitalis per gram of body weight, suspended in Clark's solution. When this type of curve is shown, recovery is not obtained by several washings of the heart with Clark's solution. Charts 2 to 4 demonstrate a typical digitalis effect produced by concentrated edema fluid from the pleurae, peritoneum and leg respectively, of digitalized patients. Attempts to obtain recovery of these hearts was not possible with repeated washings with Clark's solution.

Chart 5 shows the curve obtained when 1,250 cc of peritoneal fluid was used which had been obtained from a patient with an abdominal malignant growth for whom, at the time all the factors of digitalization were not known. Frequent paracentesis for ascites due to the ovarian malignant growth with peritoneal metastases had been carried

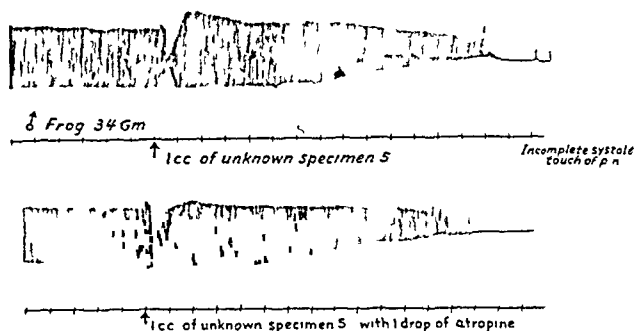


Chart 2—The upper curve shows the effect on a Straub preparation of the heart of 1,100 cc of concentrated pleural fluid from a digitalized patient. The lower curve shows a persistent digitalis effect, unchanged by the addition of a drop of weak solution of atropine.

out, and on one occasion when the patient was admitted to the hospital digitalis was given because of an element of myocardial insufficiency. The fluid obtained for this study was known to have accumulated after digitalization, but the patient's interval history was incoherent regarding the daily use of the drug. The fluid showed a typical digitalis effect. After the heart had come to a systolic standstill, the apex was touched with the point of a pin, which produced a more complete systole, shown at the end of the graph. This procedure, suggested to us by Dr Hunt, gave further evidence of a digitalis effect, since it was impossible to obtain any recovery by repeated washing of the heart. At the time this abdominal fluid was obtained it was included in the group of questionably "digitalized fluids," because of the inadequate history. However, later information from relatives of the patient revealed that she had been given digitalis regularly. Therefore the patient is now included in the group of digitalized patients.

Certain of the curves suggested in places a choline effect, but it seemed unlikely from the method used that any choline might be present.¹⁸ Several experiments in which choline was used were performed under the same conditions but they did not yield curves like the ones we were getting. Moreover, small doses of atropine (which neither stimulate nor depress the cardiac muscle) will inhibit all the action of choline¹⁹ but not that of digitalis.²⁰ Several drops of weak atropine added to the solutions tested had no influence on the type of curve obtained. Further, the presence of choline could not be detected in any of the substances under study by the chemical tests devised by Booth.²¹

In addition, it was questioned whether the curves observed could be due to the effect of calcium. Although McLean, Hastings²² and others have pointed out the typical effect of calcium on the Straub preparation of the heart it has been maintained by Loewi (quoted by Cloetta²³) that the action of calcium is similar to that of digitalis, that there can be no action of digitalis without calcium and that the effects of calcium and of digitalis are to be considered as identical. However, Cloetta and Fischer²⁴ have shown that one can abolish a calcium effect

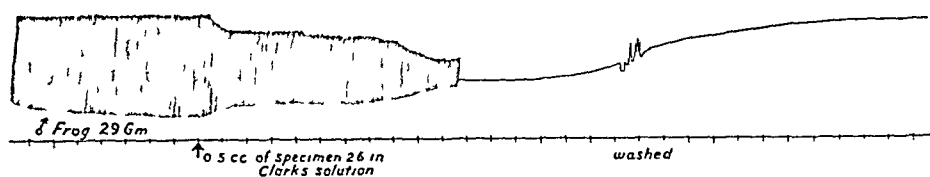


Chart 3—The effect on a Straub preparation of the heart of 6,300 cc of concentrated ascitic fluid in Clark's solution. Note the failure of recovery after washing and the complete systolic standstill.

by rinsing the heart, but not a digitalis effect, so the two are not identical. In control curves, when calcium was used, complete recovery was always obtained by washing, in no instance in which we obtained a

18 Hunt, R. Personal communication to the authors. Hastings, A. B. Personal communication to the authors.

19 Hunt, R. Some Physiological Actions of the Homocholins and of Some of Their Derivatives, *J Pharmacol & Exper Therap* **6** 477, 1914-1915, Vaso-dilator Reactions, *Am J Physiol* **45** 197 and 331, 1918.

20 Edmunds, C. W., and Gunn, J. A., in Cushny, A. R. A Textbook of Pharmacology and Therapeutics, Philadelphia, Lea & Febiger, 1928, p. 443.

21 Booth, F. J. A Microchemical Test for Choline and Its Esters in Tissue Extracts, *Biochem J* **29** 2064, 1935.

22 McLean, F. C., and Hastings, A. B. Biological Method for Estimation of Calcium Ion Concentration, *J Biol Chem* **107** 337, 1934.

23 Cloetta, M. The Biochemical Action of Digitalis, *J A M A* **93** 1462 (Nov. 9) 1929.

24 Fischer, H. Beitrag zur Frage des Synergismus zwischen Digitalis- und Calciumwirkung, *Arch f exper Path u Pharmacol* **130** 194, 1928.

curve that appeared to show a digitalis effect could we abolish it by rinsing

With thirteen of the eighteen specimens of fluid from known digitalized patients, positive evidence of a digitalis effect was obtained. Its presence was questionable with four. Three of these four specimens were studied at the beginning of the work, before the technic of concentration was perfected. In one instance there was no digitalis effect whatever. With the two fluids from questionably digitalized patients the results were doubtful. No response similar to the digitalis effect was obtained with any of the nine fluids from control patients who had not had any digitalis.

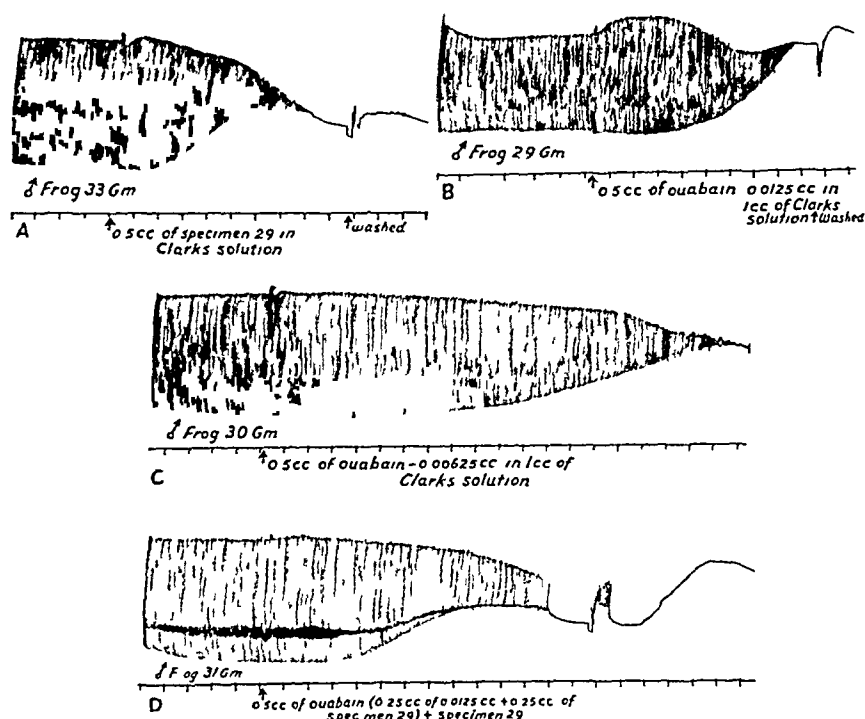


Chart 4—The combined ouabain method with a Straub preparation of the heart. *A*, the digitalis effect of 5,000 cc of concentrated edema fluid from the leg. The heart stopped in eight minutes. *B*, the typical digitalis effect of a lethal dose of ouabain. Note that the heart stopped in nine minutes. *C*, a frog of approximately the same size was given half the dose of ouabain used to produce the curve in *B*. Note that the heart stopped in twenty minutes, taking approximately twice as long as in *B*. *D*, the curve of the combined effects of *A* and *C*. Half the dose used in *A* plus the same dose of ouabain used in *C* was used in the heart of a frog of approximately the same size. Systolic standstill was produced in twelve minutes. This amount of ouabain used alone should have taken about twenty minutes (as in *C*) to stop the heart.

The direct chemical tests for the presence of digitalis bodies on the whole have proved unsatisfactory. This is in accord with the experi-

ence of others.²⁵ The various fluids were tested by the Knudson-Dresbach quantitative method²⁶ and the Kellei-Kiliani qualitative method.²⁷ With the former the results were negative, with the latter, five of eleven fluids gave positive results, all of which showed the presence of digitalis in the Straub preparation of the heart.

Finally, there is one more procedure to confirm the presence of active digitalis substances in the body fluids of digitalized patients. This consists in using the precipitate obtained by the chemical means, suspended in Clark's solution, combined with a sublethal dose of digitalis—the so-called combined ouabain method of Hatcher.²⁸ Into the ventral lymph sac of a live frog is injected a fraction of a known lethal dose of ouabain, the unknown substance is added and it is noted whether the combined action of the two substances gives a lethal digitalis

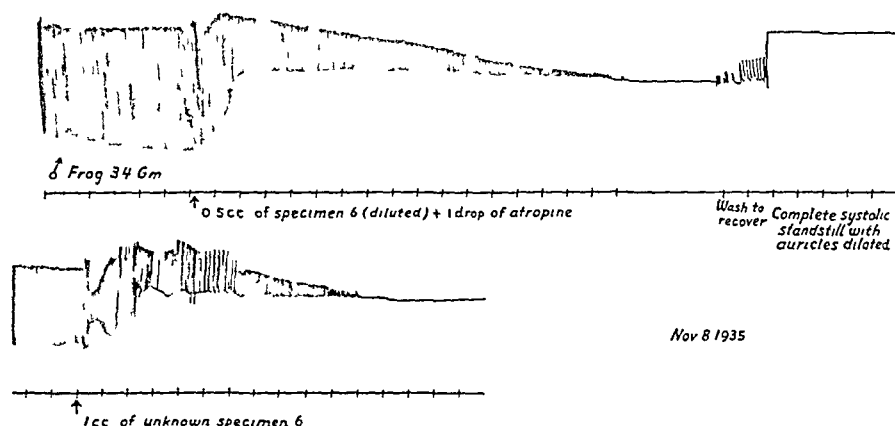


Chart 5—The digitalis effect of 1,250 cc of ascitic fluid from a digitalized patient with an abdominal malignant growth. At first there was an unsatisfactory history of treatment with digitalis. The fluid showed a typical digitalis effect, uninfluenced by atropine—complete systole with mechanical irritation. Later information revealed that there had been regular treatment with digitalis before the patient's admission to the hospital. The lower curve represents the typical digitalis effect produced by the concentrated abdominal fluid. The upper curve shows the type of curve uninfluenced by the addition of atropine. After stoppage of the heart, mechanical irritation of the ventricle (accepted in digitalis assay methods) caused a complete systolic standstill with the auricles dilated.

25 Lendle, L, and Schmelzer, W. Ueber die Baljetsche Farbreaktion der Digitaliskörper, *Arch f exper Path u Pharmakol* **177** 622, 1935. Hanzlik, P. J., and Wood, D. A. The Mechanism of Digitalis Emesis in Pigeons, *J Pharmacol & Exper Therap* **37** 67, 1929.

26 Knudson, A., and Dresbach, M. A Chemical Method of Assaying the Active Principles of Digitalis, *J Pharmacol & Exper Therap* **20** 205, 1922.

27 Koch, F. C. Practical Methods in Biochemistry, Baltimore, William Wood & Company, 1934, p. 63.

28 Hatcher, R. A. The Persistence of Action of the Digitalins, *Arch Int Med* **10** 268 (Sept) 1912.

effect. This was done in two experiments. In the first experiment half the lethal dose of ouabain was given with the unknown substance, and death of the frog did not occur. In the second experiment three fourths of the lethal dose of ouabain plus the unknown substance produced a typical cardiac systolic standstill in sixty or sixty-five minutes. The same procedure was carried out also with the Stiaub preparation of the heart, three other concentrates of edema fluid being used. As shown in chart 4, adding the unknown substance to half the lethal dose of ouabain produced a typical summation effect in about the same time required by a lethal dose of ouabain alone. This gave further evidence that the material we were recovering from the body fluids of digitalized patients was a substance that acted synergistically with ouabain as well as like digitalis.

COMMENT

The curves showing a digitalis effect obtained with fluids removed from patients who had been taking the drug, the absence of such an effect with fluids from persons who had not taken digitalis and the synergistic action seen by the "combined ouabain method" of Hatcher have led us to believe that we have been able to recover active digitalis substance from the body fluids of digitalized patients. Whether the substance recovered in these instances is the cause of postdiuretic symptoms has not been solved by this study. Its presence in the body fluid, however, adds validity to our assumption, but further studies are necessary to substantiate or to discredit the idea of digitalis intoxication with diuresis. Other studies have suggested themselves, but sufficient data have not yet been obtained.

No attempt was made to estimate accurately the amount of digitalis contained in the various fluids analyzed in this study. A rough comparison between our curves and those obtained from known strengths of digitalis led us to the opinion that as much as the equivalent of 1 cc or more of tincture of digitalis was present per liter of fluid. If this is true, it is conceivable that excretion of from 5 to 8 liters or more, which occasionally occurs within twenty-four hours after the administration of a mercury diuretic or a preparation like theophylline, may be adding as much as 0.5 Gm. or more of digitalis to an already digitalized heart. Added to cardiac muscle that is fully digitalized, such an amount of digitalis substance could easily provoke the symptoms of headache, giddiness, weakness, nausea and even vomiting.

SUMMARY AND CONCLUSIONS

A patient with cardiac disease who is digitalized and who yet shows peripheral edema or free fluid in the body cavities occasionally has symptoms of headache, nausea, vomiting, giddiness and lassitude after diuresis induced with salyrgan or mercurin or with theophylline. These

symptoms could be due to digitalis intoxication when the body fluids are excreted through the kidneys by way of the blood stream, if that body fluid contained digitalis substances

On the basis of the chemical method of Schmidt, modified in terms of the physical properties of digitoxin, edema fluid from the pleurae, peritoneum and leg was treated and concentrated, with the recovery of a gray-white precipitate. This precipitate, suspended in Clark's solution, was placed in a Straub preparation of the frog heart to be tested for digitalis, and the results were recorded on a kymogram. These curves were compared with curves for known digitalis.

A total of twenty-nine specimens of fluid from twenty-four patients were examined. Eighteen fluids were from known digitalized patients. Thirteen of these gave positive evidence of digitalis by the biologic method. The results were questionable in four cases and negative in one case. Two specimens from patients with questionable digitalization gave doubtful results. Nine specimens of fluids from patients with tuberculosis, neoplasm or cirrhosis of the liver, none of whom had been given digitalis, were used as controls. None of these showed any digitalis effect.

Although no exact quantitative determinations were carried out for the thirteen fluids showing curves indicative of a digitalis effect, we believe the amount recovered was significant and sufficient to cause clinical symptoms in patients under the conditions discussed.

The Knudson-Dresbach reaction for the quantitative determination of digitalis glucosides was unsatisfactory in our experience. The qualitative Keller-Kiliani test for desoxycarbohydrate, though not specific and not highly sensitive, gave positive reactions for five of eleven specimens of fluid showing the digitalis effect by the biologic method.

It is believed that active digitalis substances are present in the body fluids of digitalized patients and that they can be recovered. Further studies are necessary, however, to confirm or to discredit the idea that these substances may give rise to symptoms of digitalis intoxication following diuresis.

NOTE—Since this paper went to press a fully digitalized patient with poor compensation entered the hospital and after three successive administrations of salyrgan had prompt diuresis, headache and nausea (no vomiting) and twice became irrational. On two of these occasions during diuresis the electrocardiogram showed coupling during the symptoms not present before or after. During the second period of diuresis ammonium chloride was withheld, and there was a drop in the chloride content of the serum from 570 to 480 mg per hundred cubic centimeters. On the other two occasions when the salt was given, no change in the chloride value occurred, yet the symptoms were the same during all three periods of diuresis.

EFFECT OF PARENTERALLY ADMINISTERED PEPTONE

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AND

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The possibility of supplying the nitrogen requirements of the body parenterally led us to investigate the effect of protein split products given by this route. For many years reports have appeared in the literature on various phases of the phenomenon which has been designated "peptone shock." These have included elaborate chemical studies and physiologic observations made after the parenteral and oral administration of certain protein split products. This work has all been carried out with crude products of protein digestion. In consequence the results obtained have been variable and often contradictory.

REVIEW OF THE LITERATURE

In 1913 Henriques and Andersen¹ described experiments in which they maintained goats in positive nitrogen balance by means of intravenous injections. The authors achieved this by administering a solution containing completely digested (trypsin-erepsin) meat, dextrose, sodium acetate, sodium chloride, potassium chloride, calcium chloride and magnesium chloride by continuous intravenous drip. They concluded that protein synthesis can occur when these products are administered parenterally.

A year later the same authors² reported a similar experiment on a goat from which the intestinal tract had been removed, in order to prove that the gastro-intestinal tract took no part. The animal survived for three days, during which time it was shown to be in positive nitrogen balance. Further experiments with native proteins and also Witte's peptone were unsuccessful. Thompson³ concluded that parenterally administered peptone and proteose are retained to the extent of 60 per

From the Department of Pathology and the Department of Surgery, the University of Illinois College of Medicine

1 Henriques, V, and Andersen, A C *Ztschr f physiol Chem* **88** 357-369, 1913

2 Henriques, V, and Andersen, A C *Ztschr f physiol Chem* **92** 194-211, 1914

3 Thompson, W H *J Physiol* **25** 1-21 and 79-190, 1899-1900

cent He demonstrated a diuretic effect as the result of the injection with a decrease in the output of nitrogen and urea per cubic centimeter but an increase in the output of total nitrogen and urea He assumed that the proteoses were held in combination with globulin

Buglia⁴ concluded from experiments involving the intravenous injection of protein split products that amino-acids administered in this manner are burned or excreted through the kidney, their fate depending largely on the concentration of the solutions injected

Biasiotti⁵ studied the changes in the bile following the parenteral injection of Witte's peptone into dogs He concluded that it was not injurious in amounts not in excess of 0.3 Gm per kilogram if the kidneys were intact

Fink,⁶ in a study of the antigenic properties of proteoses, concluded that peptone shock is not anaphylactic and concurred with Underhill's⁷ conclusions that their effect is due to proteoses

Auld⁸ also concluded that the activity of commercial peptones is dependent on their proteose content

Gross⁹ observed that the bloody diarrhea induced by a 0.3 Gm per kilogram dose of Witte's peptone rapidly administered intravenously is prevented by atropine He concurred with other authors in ascribing the effects of Witte's peptone to the proteose present

More recently Urbach and Kitamura¹⁰ arrived at much the same conclusion On this ground they objected to the term peptone in connection with these products They further showed that the effect of peptone on the uterine strip as demonstrated by Jadassohn and Schaaf, is due to the potassium content of the solution of peptone

Clark¹¹ concluded that the toxic effects were produced by the higher proteoses (the fraction precipitated by 80 per cent alcohol)

Mills¹² found that 48 cc of a 10 per cent solution of peptone administered rapidly intravenously prevented the blood from clotting When peptone was added to the blood in vitro the reverse effect was noted The author ascribed this phenomenon to the neutralization of the thrombolytic substance in the blood, which in vivo is overcompensated

4 Buglia, G Arch di fisiol **24** 448-453, 1926

5 Biasiotti, A Arch di biol **5** 43-54, 1928, Ber f d ges Physiol **45** 783, 1928

6 Fink, E B J Infect Dis **25** 97-123, 1919

7 Underhill, F P Am J Physiol **9** 345-373, 1903

8 Auld, A G Brit M J **1** 835-836, 1922

9 Gross E G J Pharmacol & Exper Therap **30** 351-360, 1927

10 Urbach E, and Kitamura S Klin Wchnschr **13** 1573-1575, 1934

11 Clark, A J I Pharmacol & Exper Therap **23** 45-54, 1924

12 Mills C A Chinese J Physiol **1** 249-262, 1927, Am J Physiol **76** 642-650, 1926

by the pouring out of this substance following its neutralization in the blood. He compared the process to a toxin-antitoxin reaction and said he considered it to be a true immune reaction.

Feldberg,¹³ Wand¹⁴ and others observed a drop in the blood pressure with accompanying symptoms of shock following the injection of peptone. Underhill,¹⁵ on the other hand, injected a specially prepared protein split product and could demonstrate no change in blood pressure or coagulation.

Chahovitch¹⁶ demonstrated hyperglycemia following the intra-peritoneal injection of Witte's peptone. Nord¹⁷ and Henderson and Underhill¹⁸ also noted hyperglycemia following the parenteral administration of Witte's peptone.

Kaiwa¹⁹ was unable to demonstrate any change in peptone hyperglycemia in dogs following bilateral splanchnicotomy and vagotomy and sympathectomy in the upper lumbar region. Nor was he able to demonstrate any increase in epinephrine as the cause. He concluded that the hyperglycemia is peripheral in origin.

Irving and Kay²⁰ found an increase in the dextrose in the corpuscles after the intravenous injection of peptone.

In contrast to these authors, Menten and Manning²¹ found a marked variation in the effects of different samples of Witte's peptone on the sugar content of the blood, ranging from hyperglycemia to fatal hypoglycemia. McGuigan and Ross²² observed hypoglycemia after the injection of small doses of peptone.

Schiff and his co-workers²³ concluded from their experiments that anoxemia was the cause of the hyperglycemia of shock induced by Witte's peptone. They found that epinephrine given during peptone shock caused further hyperglycemia as well as a rise in blood pressure. Insulin administered during peptone shock caused a sharp drop in the sugar content of the blood and a rise in blood pressure. These workers

13 Feldberg, W. *Arch f exper Path u Pharmacol* **140** 156-167, 1928.

14 Wand, R. A. *Nature, London* **117** 487, 1926.

15 Underhill, F. P. *Am J Physiol* **9** 345-373, 1903.

16 (a) Chahovitch, X. *Arch internat de physiol* **29** 298-300, 1927. (b) Chahovitch, X., and Arnovlevitch, V. *Compt rend Soc de biol* **96** 16, 1927.

17 Nord, F. *Acta med Scandinav* **65** 1-60, 1926, *Compt rend Soc de biol* **93** 1185-1188, 1925.

18 Henderson, Y., and Underhill, F. P. *Am J Physiol* **28** 275-277, 1911.

19 Kaiwa, T. *Tohoku J Exper Med* **20** 365-388 and 471-497, 1933.

20 Irving, J. T., and Kay, H. D. *J Physiol* **61** 113-121, 1926.

21 Menten, M. L., and Manning, H. M. *J Biol Chem* **72** 255-260, 1927.

22 McGuigan, H., and Ross, E. L. *J Biol Chem* **22** 417-423, 1915, **30** 175-179, 1917.

23 Schiff, E., Eliasberg, H., and Mazzeo, A. *Pediatrics* **38** 1158-1161, 1930, *Jahrb f Kinderh* **128** 209-227, 1930, **129** 266-269, 1930, **134** 362-366, 1932.

reported also a marked lowering of the p_H and carbon dioxide content of the blood and an increase in the chloride, lactic acid, potassium and calcium contents

Garofeanu and Lazar²⁴ found that associated with the shock induced by the injection of 0.15 Gm of Witte's peptone per kilogram, the urea content of the blood was diminished in the majority of instances. Chahovitch^{16a} demonstrated a drop in the cholesterol content of the blood during the first three hours after injecting from 2.5 to 22 cc of a 5 to 20 per cent solution of peptone, followed by a rise which reached a maximum after from seventy-two to ninety-six hours.

EXPERIMENTS

It is apparent that these workers have confined their observations to the changes in peptone shock induced by the injection of crude mixtures consisting chiefly of proteose, usually in the form of Witte's peptone.²⁵ Henriques and Andersen used a somewhat more completely digested protein and may have succeeded in having it utilized, although the mere retention of nitrogen over the short period of observation reported is inconclusive.

Taking cognizance of these shortcomings in previous work on the subject, we used Difco bacto-peptone, which, according to the analysis submitted by the manufacturers, is constant in composition and contains

	Percentage
Total nitrogen	16.52
Coagulable nitrogen	None
Total proteose nitrogen	0.97
Primary proteose nitrogen (precipitable by saturation with zinc sulfate)	0.07
Secondary proteose nitrogen (precipitable by half saturation with zinc sulfate)	0.90
Peptone nitrogen	15.50
Free amino-acid nitrogen	1.69
Ammonia nitrogen	0.03
Amino nitrogen (determined by Van Slyke method)	2.32
Ash	2.87

Concentrations of 1, 5, 10, 20 and 30 per cent were used, and the solutions were carefully made up in sterile water and passed through a Berkefeld filter. A 1 per cent solution of Difco bacto-peptone is hypotonic, causing hemolysis of the red blood cells; this concentration was made up in a buffered saline solution. Since solutions of peptone give a strongly positive reaction to the biuret test, the urine was collected and examined by this method.

²⁴ Garofeanu, M., and Lazar, N. *Compt. rend. Soc. de biol.* **95**: 427-428, 1926.

²⁵ Witte's peptone is a variable mixture of proteoses with relatively small amounts of peptone.

Our problem was to determine first, the concentrations of solutions of proteose-free peptone tolerated when administered intravenously to an experimental animal, second, the effect of solutions of peptone on the excretion of urine, third, the effect of such intravenous injections on the blood and spinal fluid pressure, fourth, the effect of solutions of peptone on the chemical findings in the blood, fifth, the fate of the peptone injected, so far as that may be determined, and, sixth, whether or not Difco bacto-peptone had any antigenic effect

Two dogs were given a 20 or 30 per cent solution of peptone by the intravenous route daily in addition to a full diet. The details of this experiment are recorded in the accompanying table

Experimental Data

	Date, 1934	Concen- tration of Solution of Peptone, %	Volume, Cc	Time Taken for Injection, Minutes	Temperature		Weight, Pounds
					Before Injection, F	After Injection, F	
Dog 1	11/ 1	20	75	20			43
	11/ 3	20	300				
	11/ 4	20	300				
	11/ 5	20	300				43
	11/ 6	30	300	50	102.3	103.4	
	11/ 7	30	300	60	101.8	102.6	
	11/ 8	30	300		102.6	101.5	
	11/ 9	30	300		102.8	102.0	
	11/12	30	300		102.0	101.4	
	11/13	30	300				
	11/14	30	300				
	11/15	30	300	10	102.4	101.6	43
	11/16	30	300		102.9	102.0	
	11/17	30	300	15	101.7	101.2	
	11/19	30	300				
	11/20	30	300				
	11/21	30	300				
Dog 2	11/ 1	30	300				
	11/ 2	30	300				
	11/ 4	30	300				
	11/ 5	30	300				
	11/ 6	30	300	45	103.2	103.5	
	11/ 7	30	300				
	11/ 8	30	300		103.6	103.8	
	11/ 9	30	300		104.0	104.0	
	11/12	30	300				
	11/13	30	300				
	11/14	30	300				
	11/15	30	300	20	102.2	101.6	
	11/16	30	300		101.5	100.0	
	11/17	30	300	20	103.0	102.5	

It is apparent from the protocols that large quantities of peptone may be administered intravenously daily to dogs with no apparent deleterious effect. For the first nine days the temperature rose a maximum of up to 1 F during injection of the peptone. After the ninth day the temperature fell as much as 0.9 F during the injection. Petersen, Muller and Saelhoff²⁶ observed a similar reversal effect on the leukocytosis induced by peptone beginning on the eleventh day of the injections.

The third group of experiments was carried out to determine the effect of peptone on the blood and spinal fluid pressure.

²⁶ Petersen, W. F., Muller, E. F., and Saelhoff, C. J. *Immunol.* **19** 165-175, 1930

The blood pressure was determined by direct incannulation of the carotid artery, the fluctuations being recorded on a smoked drum. The spinal fluid pressure was obtained from a spinal needle inserted into the cisterna magna and attached to a water manometer. Direct readings were made at intervals and recorded. Peptone was injected at varying rates by means of a Woodyatt pump. Solutions of peptone of various concentrations were used.

The maximal changes in the blood pressure obtained with the concentrations of peptone used consisted of a drop in the systolic pressure of 10 mm of mercury and a rise in the diastolic pressure of 5 mm of mercury shortly after the beginning of the experiments (chart 10)

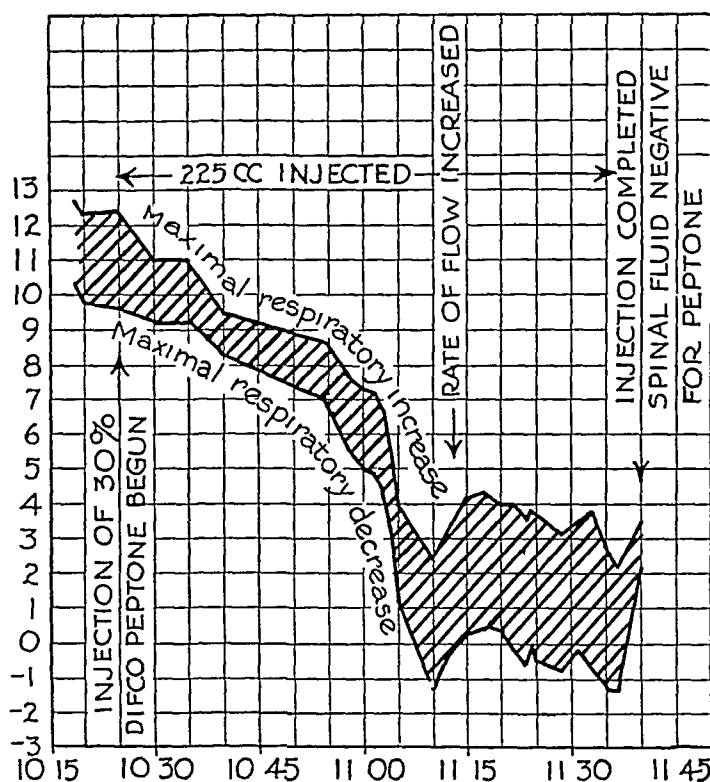


Chart 1—The spinal fluid pressure in millimeters of mercury

The spinal fluid pressure varied with the concentration of the solution of peptone. The injection of a 30 per cent solution of peptone (chart 1) resulted in a drop which was prompt and well sustained, reaching a negative value in many instances. Further, the spinal fluid in all instances gave a negative reaction to the biuret test.

Spinal fluid pressure is dependent on the osmotic balance between the blood and the tissues of the central nervous system, the freedom of circulation of the spinal fluid, the permeability of the capillaries and the venous pressure. The sharp reduction in spinal fluid pressure noted in these experiments is apparently dependent on the elevation of the osmotic pressure of the blood with resulting dehydration of the central

nervous system The absence of a secondary rise is due to the impermeability of the spinal fluid barriers to it²⁷ The diuresis may be postulated as resulting from an increase in the osmotic pressure of the blood or from the tendency of the body to excrete the peptone as a foreign material, requiring a considerable volume of water as a vehicle of excretion, or from a combination of these two factors

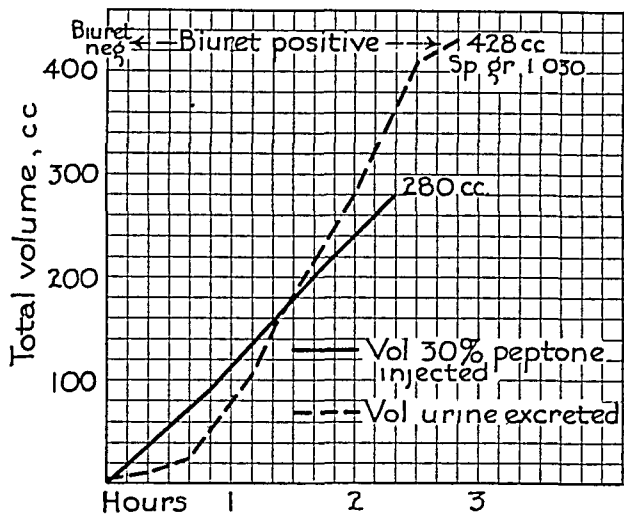


Chart 2—The effect of an injection of a 30 per cent solution of peptone on the urinary output

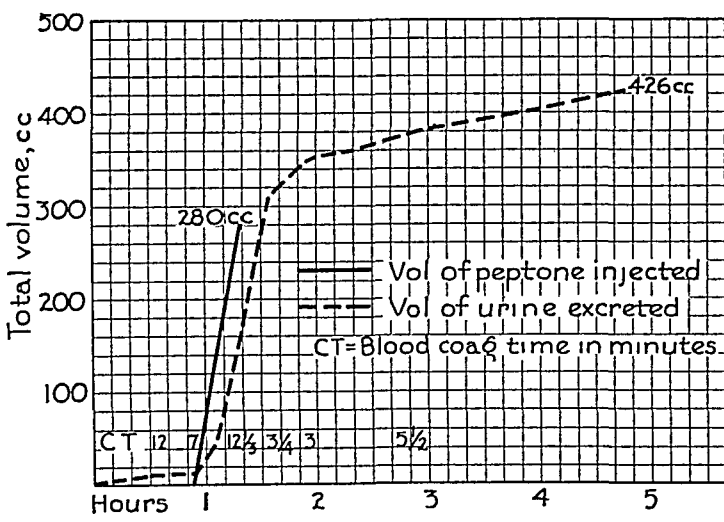


Chart 3—The effect on the urinary output of a rapid injection of a 30 per cent solution of peptone

In the second group of experiments the volume of urine excreted during the period of observation exceeded the volume of fluid injected when a 30 per cent solution of peptone was administered slowly (chart

27 Milles, G, and Hurwitz, P The Effect of Hypertonic Solutions on Cerebrospinal Fluid Pressure, with Special Reference to Secondary Rise and Tonicity, Arch Surg **24** 591-601 (April) 1932

2) Indeed, the volume of urine excreted had already crossed the line of the injected volume after one hundred minutes, i e, the output of urine exceeded the volume of injected fluid at any given moment after

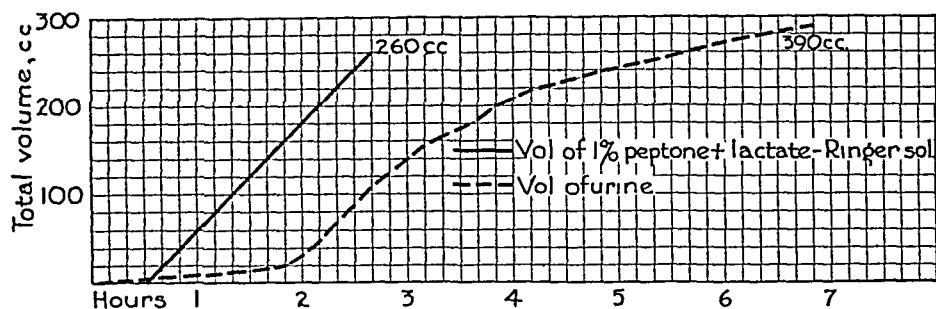


Chart 4—The effect on the urinary output of a 1 per cent solution of peptone and buffer salts

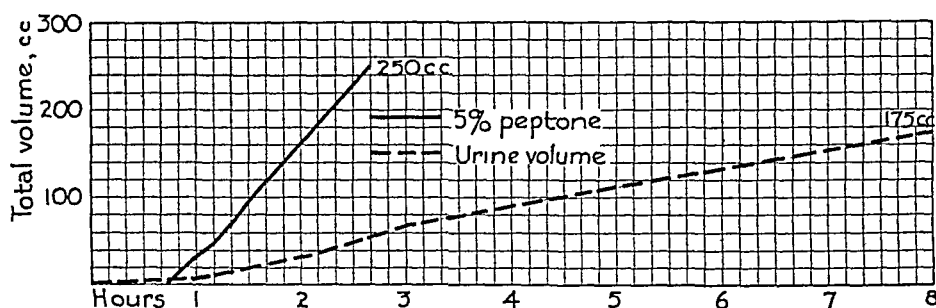


Chart 5—The effect on the urinary output of a 5 per cent solution of peptone

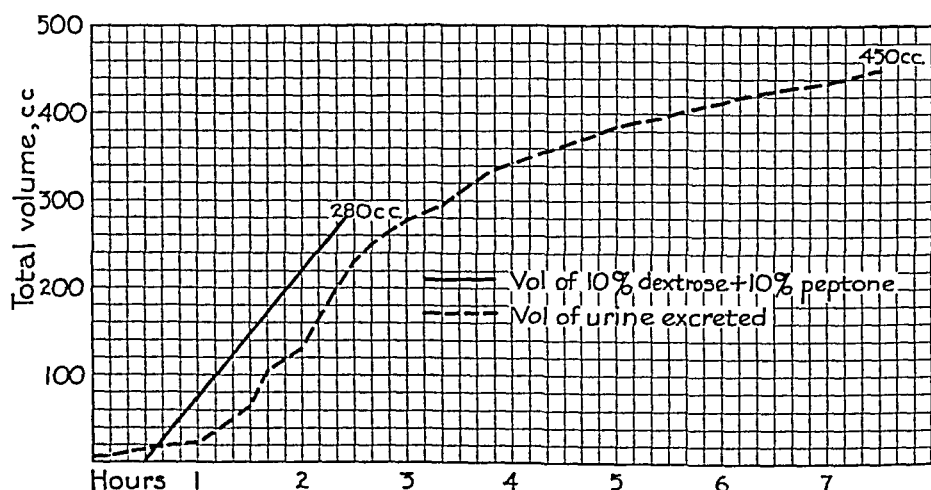


Chart 6—The effect on the urinary output of a 10 per cent solution of peptone plus a 10 per cent solution of dextrose

this time and continued to do so throughout the remainder of the experiment. When the rate of injection was rapid, the volume excreted paralleled the volume injected and did not exceed it until after the injection had been completed (chart 3)

When the injected solution contained less than 30 per cent peptone the diuretic effect was proportionately less (charts 4 to 6). However, with a 1 per cent solution of peptone in buffered saline solution, a 10 per cent solution of peptone and 10 per cent peptone in 10 per cent dextrose solution, the volume of urine excreted as shown by determinations made during the period of observation exceeded the volume of fluid injected plus the expected normal output of urine during this time. With a 5 per cent solution of peptone the volume of fluid injected was not equaled by the volume of urine during the period of observation.

The results of the chemical studies were charted for clarity (charts 7 to 10). It will be observed that the most constant features are a

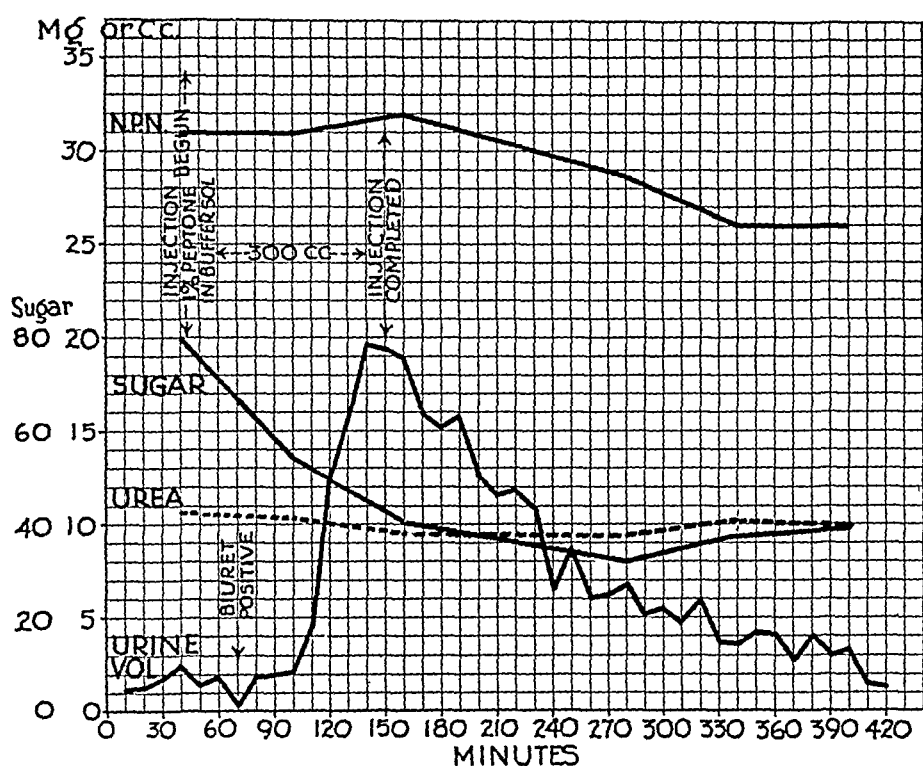


Chart 7—Results of chemical studies

primary elevation of the nonprotein nitrogen content and, to a less extent, the urea content, followed by a steady fall to a point below the original level when the experiments were closed. The sugar content of the blood tended to drop, except in the one experiment in which a 5 per cent solution of peptone was injected.

The results published here are not comparable with those of similar experiments reported in the literature, since we used a mixture of protein split products of constant composition, in no way comparable to Witte's peptone.

It was startling to find that as much as 500 cc of 30 per cent Difco bacto-peptone could be injected intravenously in many instances into a

dog with little reaction. The most marked untoward effects observed were an increased respiratory rate and vomiting. The slight rise in temperature which reversed on the ninth day to a fall, observed with daily injections of the solution, indicates a minor effect, which was possibly antigenic. The slight drop in blood pressure is indicative of a physiologic effect. When 300 cc of a 15 per cent solution of Difco

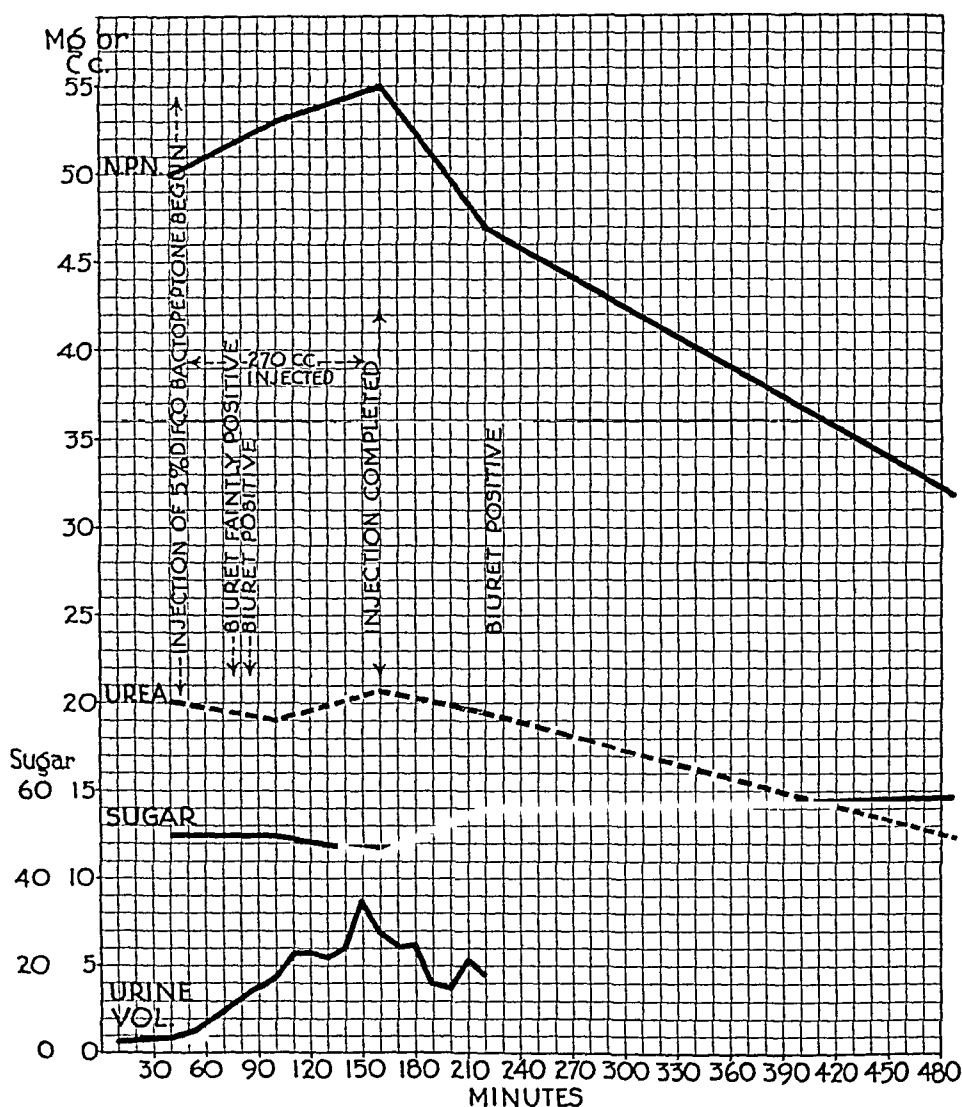


Chart 8—Results of chemical studies

bactopeptone was injected intravenously into a man, it failed to cause a reaction. However, a chill and fever resulted when a 20, 25 or 30 per cent solution was used.

The interval between the start of the injection and the appearance of peptone if we may assume that the development of a positive reaction to the biuret test of the urine is adequate proof of the presence of peptone under the conditions of the experiment, varied up to ten

minutes, the longer period being observed when a 1 per cent solution of peptone was injected. It is well known that the presence of dextrose interferes with the development of the reaction to the biuret test. In the experiment in which peptone and dextrose were injected, the urine always failed to respond to the biuret test. However, shortly after the

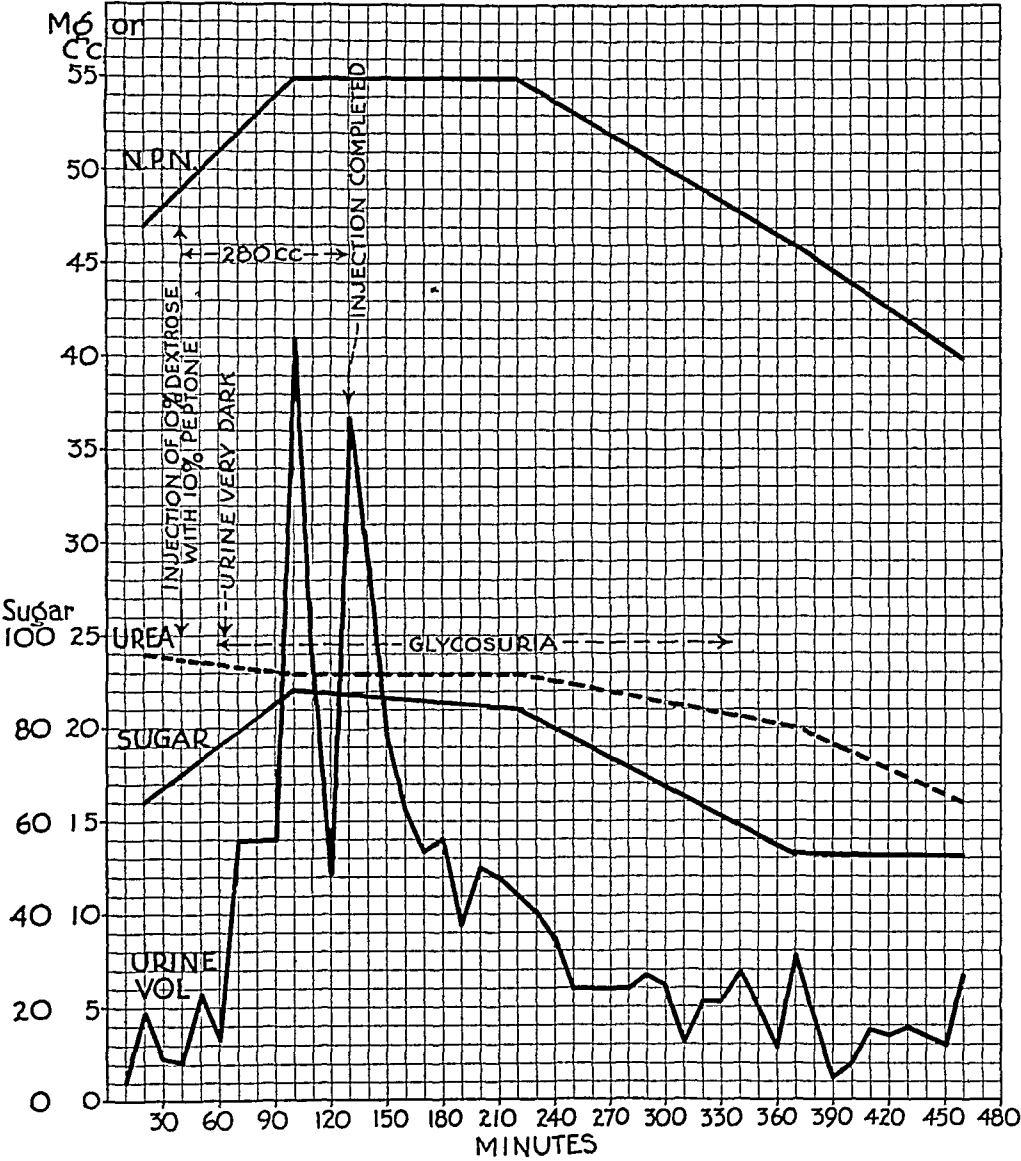


Chart 9—Results of chemical studies

start of the injection the urine became dark brown and was indistinguishable from the solution injected.

The changes noted in the blood chemistry parallel the urinary flow. They are characterized by a primary rise in the nonprotein nitrogen content, accountable for by the nitrogenous elements injected, and a secondary fall in the nonprotein nitrogen and the urea content, which is apparently merely the result of the washing out of these substances as part of the diuresis.

There are no criteria by which the utilization of parenterally injected protein split products can be determined. Henriques and Anderson assumed that the retention of nitrogen was sufficient. We cannot agree

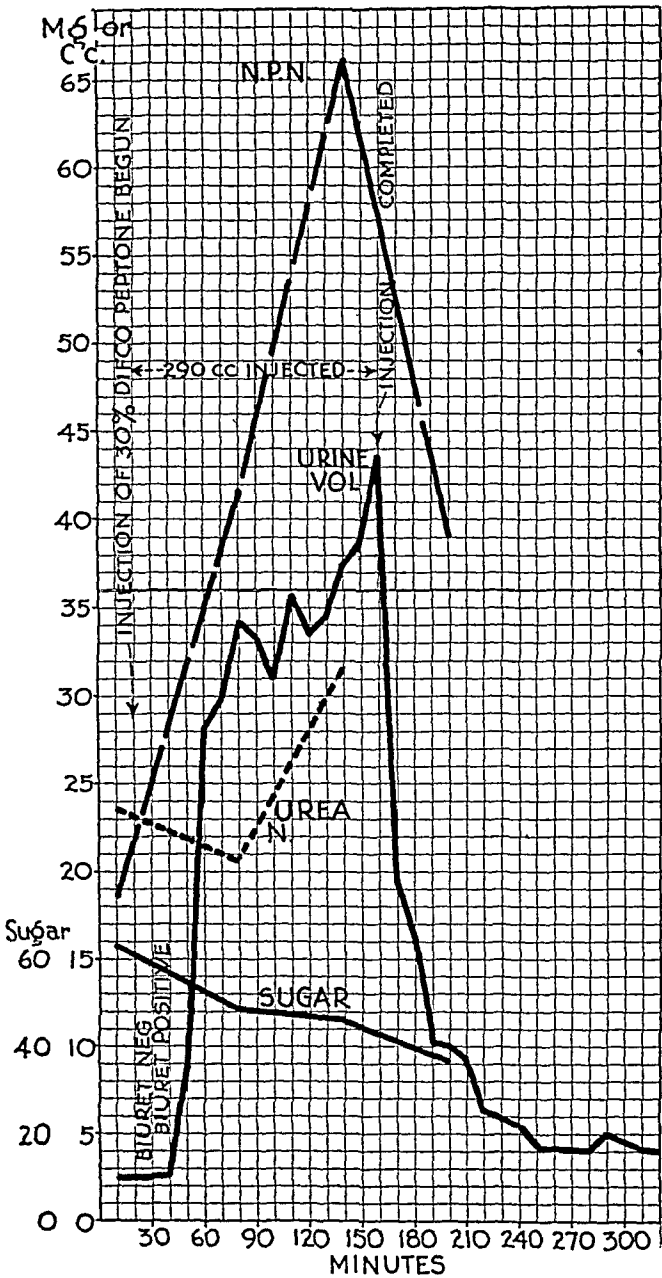


Chart 10—Results of chemical studies

with this assumption. It is possible that these products might be stored as such without utilization. Even a rise in the output of urea would in itself be inadequate evidence.

DETERMINATION OF VITAMIN C SATURATION

A FIVE HOUR TEST AFTER AN INTRAVENOUS TEST DOSE

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The response in terms of urinary excretion to a large dose of vitamin C administered orally has been widely used during the past few years as an indication of vitamin C saturation of the body¹

The amounts and the mediums (i.e., orange juice, tomato juice and crystalline vitamin C) have varied, but the method of administration has been by mouth. The possibility of error in such a test is now known to be great, owing to the variation in absorption and utilization of vitamin C from the gastro-intestinal tract as a result of varying degrees of acidity (anacidity), inflammation, the introduction of laxatives and other less understood factors. We have found this to be the case frequently². The same objection holds for tests which involve studies of the blood level after the oral administration of this substance. Moreover, the level of excretion at which continued daily doses of 1 Gm orally failed to cause any further increase and at which an intravenous dose demonstrated saturation varied widely for different persons. For example, in the case of three patients no further rise in urinary excretion could be obtained by the daily administration of 1 Gm of cevitamic acid orally after twenty-four hour levels of 385, 503 and 207 mg per hundred cubic centimeters, respectively, were reached. Four days after the oral doses were discontinued these patients

The cevitamic acid used was furnished by Merck & Co., Inc., Rahway, N. J.

From the Department of Medicine of the New York Post-Graduate Medical School and Hospital, Columbia University

1 (a) Harris, L. J., and Ray, S. N. *Lancet* **1** 71 (Jan 12) 1935. (b) Johnson, S. W., and Zila, S. S. *Biochem J* **28** 1393, 1934. (c) Abbasy, M. A., Harris, L. J., Ray, S. N., and Marrack, J. R. *Lancet* **2** 1399 (Dec 21) 1935. (d) Youmans, J. B., Corlette, M. B., Akeroyd, J. H., and Frank, H. *Am J M Sc* **191** 319, 1936. (e) Wright, I. S. *ibid* **192** 719, 1936.

2 Wright^{1c} Wright, I. S., and Lilienfeld, A. *Pharmacologic and Therapeutic Properties of Crystalline Vitamin C (Cevitamic Acid)*, with Especial Reference to Its Effects on Capillary Fragility, *Arch Int Med* **57** 241 (Feb) 1936.

excreted 900, 1,048 and 890 mg, respectively, in the first twenty-four hours after an intravenous dose of 1 Gm of cevitamic acid. Such figures indicate definite saturation, as will be demonstrated later. This illustrates the difficulty in arriving at the percentage return level of an oral dose which by itself would accurately indicate the state of vitamin C saturation.

Studies of the cevitamic acid content of the blood and urine after intravenous doses were undertaken in an endeavor to obtain more reliable

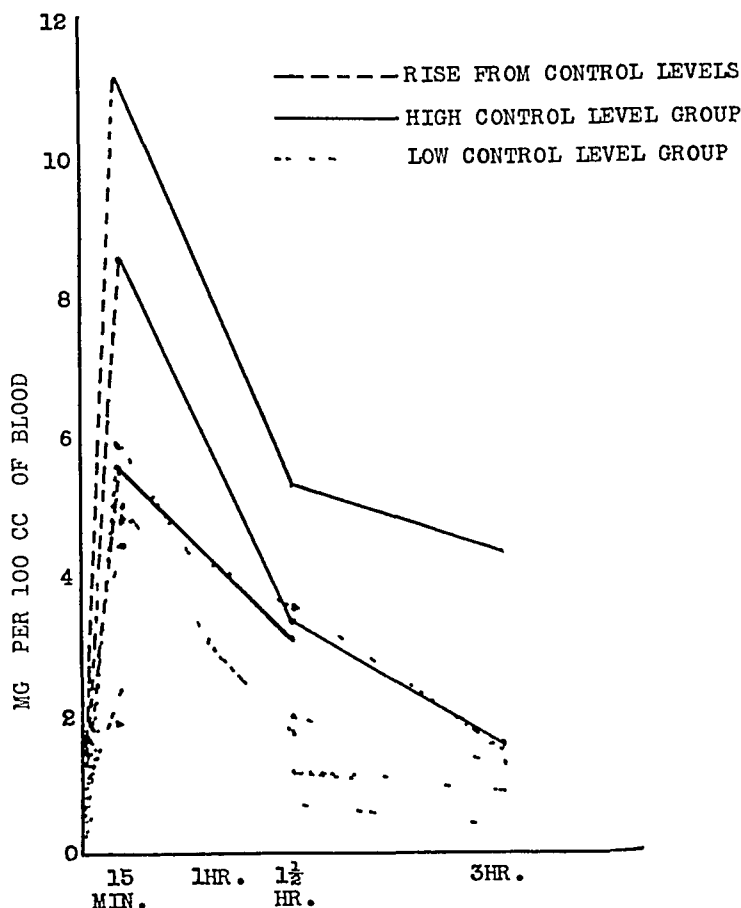


Chart 1—Typical blood curves obtained after the intravenous injection of 1 Gm of cevitamic acid

information regarding vitamin C nutrition.^{1e} It was found that after the intravenous injection of 1 Gm of cevitamic acid in 10 cc of physiologic solution of sodium chloride the cevitamic acid content of the blood reached a height which showed some relationship to the previous dietary intake and fell rapidly during the first hour and one-half, followed by a gradual return to a normal or slightly above normal level in three hours (chart 1). This drop was associated with a rise in urinary excretion, as illustrated in chart 2. In order to determine the length of

the interval between the injection of this substance and the beginning of its excretion by the kidneys the following experiment was performed with the cooperation of Dr Walter H McNeill Jr

EXPERIMENT

Ureteral catheters were introduced by means of a cystoscope into the right and left ureters of normal adults Control specimens of urine were collected One gram of cevitic acid dissolved in 10 cc of physiologic solution of sodium

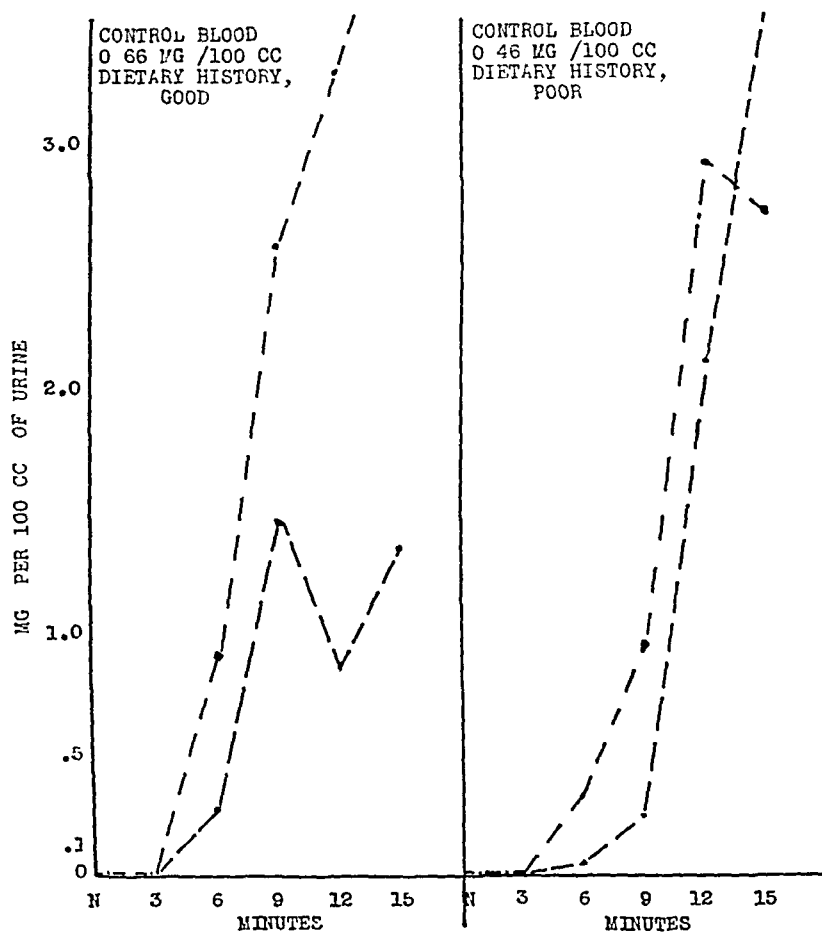


Chart 2—The urinary excretion of cevitic acid in two cases (patients G S and A McG) The dash line represents the excretion of the left kidney and the dot and dash line that of the right kidney

chloride was injected intravenously Thereafter specimens were collected from the separate ureters continuously for fifteen minutes These were divided into three minute specimens, since the amount excreted in three minutes represented about the minimum volume needed for satisfactory study

Two typical results may be seen in chart 2 The first three minute specimens failed to reveal any increase, the rise universally occurring between the third and the sixth minute A low intake of vitamin C

with a low blood level did not affect either the length of the interval or the rapidity of rise during the first fifteen minutes both being within normal limits. This rise continued until a peak was reached between the first and the second hour, after which the rate of urinary excretion likewise began to decrease. This fall was rapid until the fifth hour, by which time the major portion of the total twenty-four hour return had been excreted. Persons in a normal state of vitamin C nutrition excreted at least 500 mg of the 1 Gm test dose in the following twenty-four hours. The actual amount depended on the degree of saturation. Of the amount excreted in the twenty-four hour period,

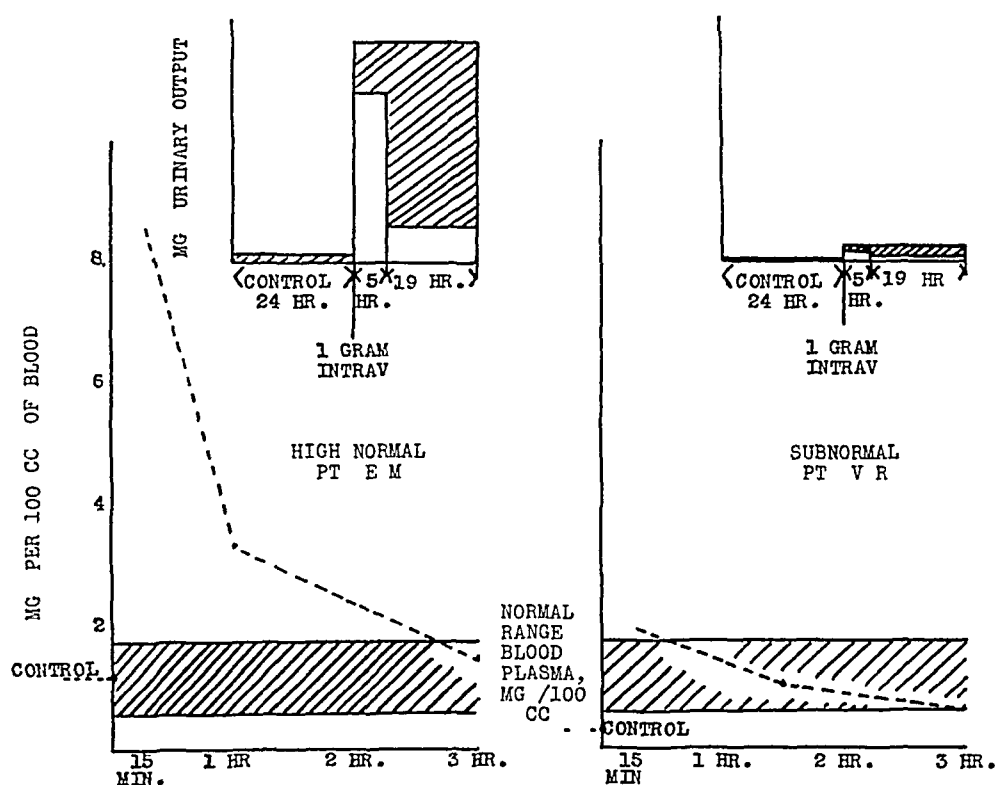


Chart 3—Comparison of the blood curve and the urinary excretion of cevitamic acid after the injection of 1 Gm of cevitamic acid for normal and subnormal persons. The total milligrams of urinary excretion indicated by the ordinates represents 1,000.

however, it was noted that 80 per cent or more was returned in the first five hours. In order to verify this observation a series of fifty-five tests were made using persons of varying degrees of vitamin C saturation.

TECHNIC

The subject was placed on a diet free from vitamin C for the twenty-four hours preceding the test and for the twenty-four hours after the administration of the test dose. During the control period the urine was collected and analyzed for excretion of vitamin C, standard precautions to prevent loss, which have been discussed in detail elsewhere,¹⁰ being used. Briefly, the specimens were col-

lected in dark brown bottles, acidified to a p_H of 3 with sulfuric acid and kept at icebox temperature. Those excreted during the day were analyzed promptly. The night specimens were analyzed early each morning. The vitamin C content was determined throughout the experiment by a modification of Tillman's³ 2,6-dichlorophenolindophenol method. At 9 o'clock on the morning of the test the patient voided, and immediately afterward 1 Gm of cevitamic acid in 10 cc of physiologic solution of sodium chloride was injected intravenously. The patient limited his fluid intake to the amount normally consumed at mealtimes, although the amount of urine excreted within the usual limits of fluctuation does not appear to affect the excretion of vitamin C. All urine passed during the first five hours after the injection was collected, including a specimen voided at exactly 2 p m. This was immediately titrated for its vitamin C content. The remaining nineteen hour specimen was collected, with the precautions previously outlined, and titrated the next morning, immediately after the 9 a m specimen had been voided.

The results of six of the experiments were discarded as unsatisfactory. The results for the remaining forty-nine patients are presented in the accompanying table. A study of this table reveals certain interesting findings. In general, the patients with the best dietary history, control blood level and control twenty-four hour urinary excretion gave the highest responses to five hour and twenty-four hour tests. As the history and control findings were increasingly subnormal, the response to the test was proportionately less satisfactory. If such findings were consistent, the question might be raised as to the need for such a test. The data for patients 36, 37 and 38 may be mentioned as answering this question. As noted, the immediate dietary history was recorded as "fair to good" for the first two and "fair" for the last one. Inquiry revealed that each of these three patients, all with gastrointestinal disorders, had been on a limited diet for one week or less, long enough for the blood content and urinary excretion to drop to low levels, but the test dose demonstrated that marked tissue unsaturation had not as yet taken place. Thus, in our opinion, the first two figures may often be misleading regarding the actual state of vitamin C nutrition of the tissues, since they are subject to sudden fluctuations after temporary dietary changes. In only two other instances (patients 22 and 24) was the five hour excretion higher than was expected on the basis of the controlled studies. These readings were slightly over 400 mg for the excretion in five hours (the low normal level). The nutrition of the tissues may have been better than we could determine by other methods. All except three patients excreted 80 per cent or more of their twenty-four hour output in the first five hours. These three excreted 75 per cent or more and all fell within the normal group, excreting 400 mg or more in five hours.

³ Tillman, J. Hirsch, P., and Jackisch, J. *Ztschr f Untersuch d Lebensmitt* 63:241, 1932.

It has been shown that fever per se produces a decrease in the excretion of vitamin C, probably because of increased metabolic demands. Persons with fever were found in all the nutritional groups in our series.

Data for Forty-Nine Patients

Vitamin C						
Patient	Dietary History	Control Blood, Mg per 100 Cc	Urine			Excretion, Percentage*
			Control Specimen, Mg per 100 Cc	5 Hour Specimen, Mg per 100 Cc	24 Hour Specimen, Mg per 100 Cc	
1	Excellent	1.54	35.90	811.34	1,048.91	77.7
2	Good	1.40	36.00	809.65	900.50	89.9
3	Good	1.20	18.00	659.10	802.00	82.4
4	Good	1.10	10.00	536.49	634.68	84.5
5	Good	1.03	19.00	441.07	559.10	78.8
6	Good	1.01		548.00		
7	Good	1.01	24.00	706.00	827.00	85.4
8	Good	0.93		832.00	956.00	86.0
9	Good	0.90	18.00	407.60	485.80	83.8
10	Good	0.84	23.00	598.00	740.00	80.0
11	Fair	0.73	20.00	553.50	573.40	96.5
12	Fair	0.72	27.20	432.20	578.30	75.0
13		0.71		442.00	511.00	86.2
Low Normal Level						
14		0.68		315.00	337.00	93.5
15	Fair	0.68	10.70	361.95	374.85	96.5
16	Poor	0.68			360.80	
17	Poor	0.67	10.40	254.30	261.00	97.0
18	Poor	0.67		221.00	241.00	91.7
19	Poor	0.65		389.00	411.00	94.7
20	Fair	0.63	15.00	351.00		
21	Fair	0.61	17.00	346.00	375.00	92.1
22	Fair	0.57	14.50	413.50	467.90	92.3
23	Poor	0.59		270.00	283.00	95.4
24	Fair	0.55	7.95	405.00		
25	Poor	0.54	13.50	207.40	244.31	84.9
26	Poor	0.52	14.00	297.00	307.00	96.6
27	Poor	0.52		235.00	241.00	97.9
28	Fair	0.51	14.80	222.60	235.90	94.3
29	Poor	0.49	13.00	286.00		
30	Poor	0.47	19.00	297.00	311.00	95.2
31	Poor	0.46	11.00	227.00	238.00	95.3
32	Poor	0.45	12.50	135.10	144.30	93.6
33	Poor	0.44	13.60	99.12	116.67	83.2
34	Poor	0.43		264.00		
35	Fair	0.42		292.64	300.60	97.3
36	Fair to good	0.41	12.00	443.00	511.00	86.7
37	Fair to good	0.41	10.00	335.00	360.00	93.1
38	Fair	0.39	9.90	404.00	415.00	96.0
39		0.39		288.00		
40	Poor	0.39	18.50	189.10	197.87	93.0
41	Poor	0.39		95.00		
42	Poor	0.39	3.00	68.00	69.00	98.0
43	Poor	0.37	3.00	160.00		
44	Good	0.37		76.00	89.00	84.6
45	Fair	0.35	11.00	168.00	185.00	91.1
46	Poor	0.34	18.80	143.57	162.70	88.0
47	Good	0.31	10.00	70.00	81.00	85.5
48	Poor	0.29		118.00		
49	Poor	0.27		68.00		

* The proportion of the twenty four hour excretion obtained in the first five hours

COMMENT

In eliminating the uncertainties of gastro-intestinal absorption and utilization, one major factor of error in determining vitamin C saturation in the body has been eliminated. The experiments outlined give definite knowledge of the subject's nutritional state with regard to

vitamin C in five hours, as compared with twenty-four hours. This has obvious advantages, such as its adaptability to ambulatory patients and as an aid when storage facilities, incontinence and poor cooperation are factors. Test doses of various sizes have been considered carefully, and 1 Gm. has been utilized for the following reasons. The size of this dose is such as to reduce the percentage of error in the actual titration when the figures are low. The figures are high enough so that slight variations in the dietary intake of vitamin C immediately preceding or during the test will produce only inconsequential effects on the results. The patient may even continue his normal diet without producing important changes in the results. The smaller the dose used, the greater the relative error introduced by the aforementioned factors. The problem of toxicity has also been considered. Thus far we have noted no evidence of toxicity or untoward effects following the injection of five hundred doses of 1 Gm. or more of cevitic acid intravenously. One gram doses have been given daily for a month, and a number of doses of 5 Gm. each have been given with only one mild thermal reaction so far recorded. In that instance we were not sure that the cevitic acid was responsible for the fever. There is therefore no known contraindication against 1 Gm. test doses thus far.

We therefore suggest the following technic for a five hour test for vitamin C saturation.

Have the patient omit breakfast, void and discard the preliminary urine and receive the test dose of 1 Gm. of cevitic acid in 10 cc. of physiologic solution of sodium chloride intravenously. Collect all the urine voided during the first five hours including a specimen voided exactly at the end of the fifth hour. The technic of preservation and of titration have already been discussed. Titration should be done as soon after the five hour period as possible to avoid undue loss of the vitamin.

While such tests, using the urinary excretion after the intravenous injection of cevitic acid, represent a distinct improvement over the oral test dose method, in that variations in absorption and utilization from the intestinal tract are eliminated, one is still confronted by the possibilities of variations in excretion due to impaired renal function and other factors of which there is little knowledge. For example if the urinary output of vitamin C is low after the intravenous test dose we have found in general that it indicates poor vitamin C saturation. It may mean in some rare instances that the excretory ability is poor. From the urine alone one cannot make a differentiation in such a case. If the blood curve⁴ is studied at the same time, as indicated in

4 The studies of the blood in this work were carried out according to the method of Farmer and Abt (Farmer, C. J., and Abt, A. *Proc. Soc. Exper. Biol. & Med.* **32** 1625, 1935).

chart 1, a differentiation may be made, since if the rate of excretion is retarded for any reason the elevation of the blood level will of necessity be prolonged, with a slower return to a normal level. More detailed studies of patients with varying types and degrees of renal damage must be made before this aspect of the problem will be understood.

It should be pointed out that tests of this type are not to be considered as indicating the presence or absence of scurvy. As previously noted,^{1e} the state of unsaturation, as indicated by chemical studies of the blood and urine, may be present for a long time without the development of scurvy. On the other hand, saturation may be chemically achieved while the manifestations of scurvy are still present, although this state will not continue long. We believe that increased capillary fragility still remains the earliest definite evidence of scurvy. It should not, however, be regarded as pathognomonic of that disease.

SUMMARY

A five hour test, made after the intravenous injection of 1 Gm of cevitamic acid, to determine the degree of vitamin C saturation in the body is proposed.

Studies are reported which demonstrate that 500 mg or more of the 1 Gm dose is normally excreted in the first twenty-four hours and that 400 mg or more (80 per cent) of that is excreted in the first five hours.

This test gives, in our experience, a more reliable estimation of the actual state of vitamin C saturation in the body than any other method hitherto available. Studies of the blood, as outlined, may be made coincidentally for additional information.

In addition, this method presents the obvious advantages of a five hour test suitable for ambulatory patients and for daily hospital use as a routine.

FUNICULAR DEGENERATION OF THE SPINAL CORD WITHOUT PERNICIOUS ANEMIA

NEUROLOGIC ASPECTS OF SPRUE, NONTROPICAL SPRUE AND
IDIOPATHIC STEATORRHEA

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Subacute combined degeneration of the spinal cord has come to involve a major problem that centers about the type of degeneration seen typically in pernicious anemia. More than sixty associated conditions or causes have been advanced for combined degeneration that often is said to be "just like that of pernicious anemia" (table 1). In some instances involvement of posterior and lateral columns, regardless of the absence of the usual status spongiosus or the presence of prominent fibrillar gliosis fills the requirement of "like", in others an occasional focus of perivascular demyelination, regardless of its nature or topography, or degeneration of the posterior roots with secondary degeneration in the posterior column suffices, too much confidence may be placed in a typical or suggestive clinical picture of combined degeneration, or an unusual clinical picture may pass without comment. Criteria needed to rule out pernicious anemia or some kindred disturbance often are left unmentioned.

The typical picture in an unusual setting is almost unique and always suggests pernicious anemia in disguise. The legitimate and important question has been raised before as to the accuracy and implications of some of these observations and as to whether the typical clinical and pathologic picture does not carry with it an import that in some manner attaches specifically to a factor unknown but commonly associated with pernicious anemia. Bremer¹ has aptly said that the greatest industry on the part of a reviewer will not permit a critical review of the subject. Numerous investigators have attempted to penetrate the problem accen-

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1. Bremer, F. W. III. Zentralnervensystem und perniziöse Anämie, *Ergebnisse d. inn. Med. u. Kinderh.* 41: 143-201, 1931.

tuated by the remarkable discovery of the unique therapeutic value of liver by Minot and Murphy in 1926²

The subject may be presented more pointedly by hazarding a few comments concerning the conditions with which subacute combined degeneration of the spinal cord has been associated or to which it has been attributed. These have been listed, for the sake of convenience, under several headings.

TABLE 1—*Conditions Associated with or Frequently Considered to Be the Cause of Subacute Combined Degeneration of the Spinal Cord "Like That Seen in Pernicious Anemia"*

Endocrine Dysfunction	Infectious Diseases	Nutritional Disorders*	Poisoning	Miscellaneous Diseases
Acromegaly	Respiratory diseases	Alcoholism	Absinth	Anemia, splenic
Addison's disease	Chorea	Beriberi	Arsenic	Anemia, secondary
Diabetes mellitus	Diphtheria	Dysentery	Barium	Amyotrophic lateral sclerosis
Exophthalmic goiter	Erysipelas	Gastric carcinoma	Chloral	Ancylostomiasis
Myxedema	Influenza	Obstruction of bowel	Ergot	Arteriosclerosis
	Malaria	Carcinoma of pancreas	Lathyrus	Infestation with Bothriocephalus
	Measles	Pancreatitis	Lead	Caisson disease
	Leprosy	Pernicious anemia	Morphine	Icterus, hemolytic
	Rabies	"Prepernicious" anemia	Phosphorus	Jaundice
	Scarlet fever		Phosphin	Leukemia
	Sepsis		Strychnine	Nephritis
	Smallpox		Tea	Pregnancy
	Syphilis	Pellagra		Primary degeneration
	Tetanus	Scurvy		Senility
	Typhoid	Sprue		Shock
	Typhus			Unclassified disease
	Tuberculosis			

* Or those in which there may be an associated nutritional factor

ENDOCRINE DISORDERS

In a patient with Addison's disease with signs of subacute combined degeneration of the spinal cord Hurst and Bell³ found hematologic changes of pernicious anemia, and they said they regarded the anemia as underlying the neurologic picture in these cases. Maestrini⁴ did not put it so clearly in reporting a case of acromegaly associated with pernicious anemia and combined degeneration but stressed a pluriglandular relationship.

Changes in the spinal cord that are associated with diabetes, although long under scrutiny, are still imperfectly understood. Changes in the

2 Minot, G. R., and Murphy, W. P. Treatment of Pernicious Anemia by a Special Diet, *J. A. M. A.* **87**: 470-476 (Aug. 14) 1926.

3 Hurst, A. F., and Bell, J. R. The Pathogenesis of Subacute Combined Degeneration of the Spinal Cord, with Special Reference to Its Connection with Addison's (Pernicious) Anaemia, Achlorhydria and Intestinal Infection, *Bram* **45**: 266-281 (Oct.) 1922.

4 Maestrini, D. Syndrome neuro-anemica in acromegalica, *Fisiol. e med.* **3**: 695-708, 1932.

posterior columns⁵ changes in the posterior and lateral columns⁶ and changes in the posterior, lateral and anterior columns of the spinal cord⁷ have been observed in cases of diabetes. Williamson^{5b} and Schweiger¹⁰ found degeneration in the intramedullary portion of the posterior roots of the spinal nerves in cases of diabetes and regarded the changes in the posterior columns as secondary. Czoniczer⁸ reported a case in which diabetes was complicated by funicular myelitis. The neurologic changes in this case were similar to those which occur in cases of pernicious anemia. Vibratory sensibility was not mentioned, and there was no report of a gastric analysis. The changes which were illustrated suggested those seen in the spinal cord in cases of pernicious anemia, but the clinical symptoms seemed to outweigh the pathologic features noted in the spinal cord. The gray as well as the white matter was involved. The results of examination of the peripheral nerves were not reported. In the case of diabetes reported by Schwab and Schwab⁹ combined degeneration of the spinal cord, Parkinson's syn-

5 (a) Bramwell, Byrom. Diabetes. Perforating Ulcer of the Foot, Advanced Atheroma of the Posterior Tibial Artery, the Artery Being Adherent to the Posterior Tibial Nerve, Marked Changes in the Posterior Tibial and Plantar Nerves, *Clin Studies* **5** 279-290 1907. (b) Hensay, Joseph. Untersuchungen des Central-Nervensystems bei Diabetes mellitus, Strassburg, C & J Goeller 1897. (c) Kalmus, Ernst. Beitrag zur Kenntnis der Rückenmarkserkrankungen bei Diabetes mellitus, *Ztschr f klin Med* **30** 559-572, 1896. (d) Sandmeyer, Wilhelm. Beitrag zur pathologischen Anatomie des Diabetes mellitus, *Deutsches Arch f klin Med* **50** 381-392, 1892. (e) Schweiger, L. Ueber die tabiformen Veränderungen der Hinterstränge beim Diabetes, *Arb a d neurol Inst a d Wien Univ* **14** 391-405, 1908. (f) Souques, A., and Marinesco, G. Lésions de la moelle épinière dans un cas de diabète sucré, *Rev neurol* **5** 242-245, 1897. (g) Williamson, R. T. Changes in the Posterior Columns of the Spinal Cord in Diabetes Mellitus, *Brit M J* **1** 398-399 (Feb 24) 1894, (h) Changes in the Spinal Cord in Diabetes Mellitus, *ibid* **1** 122-123 (Jan 16) 1904, The Symptoms Due to Peripheral Neuritis or Spinal Lesions in Diabetes Mellitus, *Rev Neurol & Psychiat* **5** 550-556, 1907, Diseases of the Spinal Cord, London, Frowde, Hodder and Stoughton, 1908, p 371, footnote 3, reference 2.

6 Leyden. Bemerkungen über Diabetes mellitus, *Deutsches Med-Ztg* **14** 497-500 and 507-511, 1893.

7 Leichtentritt, Heinrich. Ein Beitrag zur Erkrankung peripherer Nerven und des Rückenmarks bei Diabetes mellitus, Berlin, G. Schade, 1893. Nonne, M. Ueber Poliomyelitis anterior chronica als Ursache einer chronisch-progressiven atrophischen Lahmung bei Diabetes mellitus, *Berl klin Wchnschr* **33** 207-212 (March 9) 1896. Ossokine, N. Contribution à l'étude de l'anatomie pathologique de la moelle dans le diabète sucré, *abstr*, *Rev neurol* **10** 993, 1902.

8 Czoniczer, Gabriel. Ein mit Myelitis funicularis komplizierter Fall von Diabetes, *Deutsche Ztschr f Nervenhe* **104** 286-296 (Aug) 1928.

9 Schwab, S. I. and Schwab, R. S. Pernicious Anemia and Combined System Disease with Diabetes Mellitus and Parkinsonian Syndrome, *Arch Neurol & Psychiat* **35** 126-130 (Jan) 1936.

drome and pernicious anemia also were present. Some of the most severe disabilities of a neurologic order that we have observed in cases of diabetes included great weakness in the proximal muscles of the limbs, incontinence of urine and an increase in the amount of protein in the spinal fluid. The pathogenesis of these findings is unknown to us. Degeneration of the peripheral nerves, presumably on an arteriosclerotic basis, appears to be the most common neurologic feature associated with diabetes.¹⁰

Schilling's¹¹ patient with funicular myelitis and exophthalmic goiter recovered after thyroidectomy. Vibratory sensibility and the results of gastric analysis and hematologic examination were not mentioned. We have observed several patients who showed myxedema associated with observations that suggested involvement of the posterior and lateral funiculi, the patients improved as a result of treatment with thyroid preparations. There is no report of a necropsy in any of these cases.

INFECTIOUS DISEASES

Munch-Petersen¹² reported a case of a condition for which he preferred the designation encephalomyelitis funicularis infectiosa and in which the clinical symptoms and signs resembled those found in pernicious anemia. The hematologic picture was not that of pernicious anemia. The results of gastric analysis were not included. Necropsy disclosed marked degeneration of the posterior columns, including the portion adjacent to the posterior horns, which may have resulted from degeneration of the posterior roots of the spinal nerves. Degeneration of the pyramidal and cerebellar tracts, perivascular lymphocytic infiltration of both white and gray matter and degeneration of the anterior horn cells were also noted. Many different viruses may produce this picture. Perivascular demyelination is not uncommon in a number of the virus diseases. Munch-Petersen expressed the opinion, as did Bremer, that paresthesias of the hands and feet, which were present, are characteristic of involvement of the posterior column of the spinal cord. However this may be, paresthesias with degeneration of the peripheral nerves and without degeneration in the spinal cord have been observed in cases of pernicious anemia by Hamilton and Nixon.¹³

10 Woltman, H. W., and Wilder, R. M. Diabetes Mellitus. Pathologic Changes in the Spinal Cord and Peripheral Nerves, *Arch Int Med* **44** 576-603 (Oct.) 1929.

11 Schilling, Erich. Ein Fall von Myelitis funicularis bei Basedowscher Krankheit, *Deutsche Ztschr f Nervenhe* **91** 296-299 (May) 1926.

12 Munch-Petersen, C. J. Encephalomyelitis disseminata (Redlich) und Encephalomyelitis funicularis infectiosa, *Ztschr f d ges Neurol u Psychiat* **150** 451-492, 1934.

13 Hamilton, A. S., and Nixon, C. E. Sensory Changes in the Subacute Combined Degeneration of Pernicious Anemia, *Arch Neurol & Psychiat* **6** 1-31 (July) 1921.

Perivascular demyelination nests of glia cells, "fleabite" hemorrhages and thrombosis of small vessels are not uncommonly observed in infectious diseases of various kinds and may occur in the spinal cord as well as in the brain

For many of the diseases listed, no reference is given. One of Duick's¹⁴ articles is often referred to as proving that combined degeneration of the spinal cord like that which is seen in cases of pernicious anemia, may be caused by malaria. In the first of these articles Duick described purpuric hemorrhages and *Ringwallherdchen* as occurring in certain parts of the central nervous system in a number of diseases, and in speaking of typhus he included involvement of the spinal cord. In the second article, which dealt with malaria specifically, he did not mention the spinal cord at all. Malarial encephalitis, he observed, may present the clinical picture of multiple sclerosis.

Scherer¹⁵ described an unusual illness of 5 monkeys. The pathologic picture resembled that of the combined degeneration of the spinal cord that is associated with pernicious anemia. The striking feature was the epidemic onset with diarrhea. Since the disease did not affect man and the exact nature of the condition remained in doubt, this excellent report is only mentioned in passing.

NUTRITIONAL DISTURBANCES

The conditions placed tentatively under nutritional disturbances bid fair to throw light on the problem, which seems to have been brought much nearer solution by the studies of the gastric juice by Castle, Heath and Strauss,¹⁶ Greenspon,¹⁷ and others and by the response of subacute combined degeneration of the type seen in pernicious anemia to liver therapy.

14 Durck, Hermann. Die pathologische Anatomie der Malaria, München med Wchnschr **68** 33-37 (Jan 14) 1921, Veränderungen im Zentralnervensystem bei Infektions-, Intoxikations- und Blutkrankheiten, Wien klin Wchnschr **40** 181-182 (Feb 10) 1927.

15 Scherer, H. J. Funikuläre Spinalerkrankung mit schwerer Beteiligung des Grosshirnmarkes und Opticusveränderungen bei fünf Pavianen, Ztschr f d ges Neurol u Psychiat **141** 212-234, 1932.

16 Castle, W. B., Heath, C. W., and Strauss, M. B. Observations on the Etiologic Relationship of Achylia Gastrica to Pernicious Anemia. IV. A Biologic Assay of the Gastric Secretion of Patients with Pernicious Anemia Having Free Hydrochloric Acid and That of Patients Without Anemia or With Hypochromic Anemia Having no Free Hydrochloric Acid, and of the Role of Intestinal Impermeability to Hematopoietic Substances in Pernicious Anemia, Am J M Sc **182** 741-764 (Dec) 1931.

17 Greenspon, E. A. The Nature of the Antipernicious Anemia Principle in Stomach. I. Method to Improve Stomach Preparations, J A M A **106** 266-271 (Jan 25) 1936.

The results of the investigations of Salus and Reimann,¹⁸ if verified, possibly may lead to the discovery of a physiologic principle of the greatest importance. These investigators determined that Castle's intrinsic factor was present in 5 cases in which the usual clinical picture of subacute combined degeneration of the spinal cord, achylia and a normal hematologic picture were observed. They determined the presence of this factor by reinforcing liver therapy with gastric juice obtained from these patients and feeding it to patients known to have pernicious anemia. They further determined that Castle's intrinsic factor was not present in 7 cases in which subacute combined degeneration, achylia and the hematologic picture of pernicious anemia were observed. They concluded that the presence of Castle's intrinsic factor bears no obligatory relationship to subacute combined degeneration of the spinal cord but is related only to the hematologic picture. They proposed the term hemogen for the hematopoietic factor and the term neurogen for the neurotrophic factor.

For years there has been a question as to whether the neurologic complications of chronic alcoholism are primarily attributable to alcohol or occur through some intermediate process. Hurst¹⁹ expressed the view that in 3 of his patients with pernicious anemia the achlorhydria may have resulted from chronic alcoholism, and strong arguments for assuming a dietary deficiency as a factor in the production of alcoholic polyneuritis were advanced by Minot, Strauss and Cobb.²⁰ Strauss²¹ allowed 10 patients who were suffering from alcoholic polyneuritis to continue their customary daily intake of spirituous liquor on condition that they consumed a well balanced diet with a high vitamin content and supplemented with yeast or its products. They were also given concentrates of vitamin B and liver extract by parenteral injection. Improvement in the polyneuritis occurred in every instance. Nonne's²²

18 Salus, Fritz, and Reimann, F. Das Castlesche Ferment und die funikuläre Spinalerkrankung. Ein Beitrag zur Pathogenese des nervösen Krankheits syndroms (VI Untersuchungen zur Leberwirkung bei der Anaemia perniciosa), *Klin Wchnschr* **13** 986-990 (July 7) 1934.

19 Hurst, A. F. La dégenérescence combinée subaigue de la moelle et ses rapports avec l'anémie pernicieuse. L'anachlorhydrie et les intoxications intestinales, *Ann de med* **24** 5-23 (June) 1928.

20 Minot, G. R., Strauss, M. B., and Cobb, Stanley. "Alcoholic" Polyneuritis. Dietary Deficiency as a Factor in Its Production, *New England J Med* **208** 1244-1249 (June 15) 1933.

21 Strauss, M. B. The Etiology of "Alcoholic" Polyneuritis, *Am J M Sc* **189** 378-382 (March) 1935.

22 Nonne, M. Ueber Myelitis intrafunicularis und über kombinierte Strangenerkrankung bei Alkoholismus chronicus. Kasuistik zur hamorrhagischen Diathese beim chronischen Alkoholismus, *Monatschr f Psychiat u Neurol* **20** 497-528, 1906.

article on subacute combined degeneration of the spinal cord in cases of chronic alcoholism is a classic. Most of his cases were on the whole so carefully described and, incidentally, his illustrations and his instructive remarks were so convincing that there is no doubt that his 6 cases fill the requirements of the familiar picture of subacute combined degeneration of the type seen in pernicious anemia. One is left somewhat in the dark, however, as to just what was meant by his recurring notation that the stomach was normal as to motor and chemical functions. The macrocytosis or hyperchromic anemia in cases 2, 4, 5 and 6 and the hyperplastic bone marrow in cases 4, 5 and 6 certainly suggested pernicious anemia, in 1 case the author himself made this diagnosis. There are three possibilities. First, the alcohol itself may have been responsible. Second, some cases of pernicious anemia inadvertently may have been included in the thousands of cases of severe chronic alcoholism, and third, some deficiency factor induced by alcoholism may have come into play. In Fleischmann's²³ series of alcoholic addicts, to which reference is often made, signs of involvement of the pyramidal tracts were prominent, but rapid recovery often occurred when the use of alcohol was discontinued. No necropsies were reported in these cases. In Ossenkopp's²⁴ case of chronic alcoholism, which also is frequently referred to the symptoms suggested multiple sclerosis but the pathologic picture could hardly be said to resemble that usually seen in pernicious anemia, and the author himself called it atypical.

The principal neuropathologic change in cases of beriberi is neuritis.²⁵ In cases 7 and 8 in the report of Durck^{25a} the posterior columns of the spinal cord were severely involved, but the involvement was perhaps suggestive of secondary degeneration. In case 7 there was a suggestion of occasional ballooning of the nerve fibers, and the cerebellar tracts were incompletely involved.

Funicular myelitis has been described as following bacillary dysentery,²⁶ but in the cases reported the clinical picture was atypical, and necropsy was not performed.

23 Fleischmann, Rudolf. Zur Lehre von der Myelitis funicularis. Ueber heilbare und abortive Formen von Myelitis funicularis, *Deutsche Ztschr f Nervenhe* **51** 402-437, 1914.

24 Ossenkopp, G. Atypische funikuläre Myelose mit Psychose bei chronischem Alkoholismus, *Deutsche Ztschr f Nervenhe* **117-119** 350-370, 1931.

25 (a) Durck, Hermann. Untersuchungen über die pathologische Anatomie der Beri-beri, ein Beitrag zur normalen und pathologischen Anatomie des peripherischen Nervensystems, *Beitr z path Anat u z allg Path*, supp 8, 1908, pp 1-176. (b) Wright, Hamilton. Changes in the Neuronal Centres in Beri-Beric Neuritis, *Brit M J* **1** 1610-1616 (June 29) 1901.

26 Menzel, Werner. Ueber zwei Fälle von Polyneuritis und funikulärer Myelose nach bazillaren Ruhr, *Deutsche Ztschr f Nervenhe* **126** 265-284, 1932.

The clinical and pathologic evidence that gastric carcinoma may have some etiologic relationship to typical subacute combined degeneration is too strong to be disregarded²⁷ That subacute combined degeneration of the spinal cord may occur with benign tumors of the stomach also has been suggested²⁸ Metastatic involvement of the roots of the spinal nerves or the spinal cord may lead to a confusing picture²⁹ The case for carcinoma of the small intestine is not so strong²⁸ The hematologic picture of pernicious anemia has been observed with carcinoma of the colon,³⁰ and in cases of carcinoma the hematologic picture of pernicious anemia has been associated with the clinical signs of subacute combined degeneration of the spinal cord³¹ The hematologic picture of pernicious anemia has been noted also in association with stricture of the small bowel,³⁰ and in some cases in which this association occurred there also were paresthesias³² In a case reported by Salus³³ stenosis of the small bowel acquired achlorhydria, a normal hematologic

27 Fisher, J A Zur Frage der Myelosen nach Tuberkulose und Carcinom, *Deutsche Ztschr f Nervenhe* **134** 300-305, 1934 Garvey, J L, and Stern, L D Combined Sclerosis of the Spinal Cord and Carcinoma of the Stomach Report of a Case, *Am J M Sc* **168** 847-852 (Dec) 1924 Lubarsch, O Ueber Rückenmarksveränderungen bei Carcinomatosen, *Ztschr f klin Med* **31** 389-415, 1897 Simpson, C K A Case of Addison's Anaemia with Subacute Combined Degeneration of the Cord Associated with Carcinoma of the Stomach, *Guy's Hosp Rep* **81** 392-406, 1931 Waterfield, R L, Shackle, J W, and Hurst, A F The Diagnosis of Addison's (Pernicious) Anaemia Two Cases of Severe Anaemia, *ibid* **73** 206-224, 1923

28 Balfour, D C, and Henderson, E F Benign Tumors of the Stomach, *Ann Surg* **85** 354-359 (March) 1927

29 Weber, F P, and Hill, T R Complete Degeneration of the Posterior Columns of the Spinal Cord with Chronic Polyneuritis in a Case of Widespread Carcinomatous Disease Elsewhere, *J Neurol & Psychopath* **14** 57-60 (July) 1933 Weil, Arthur, and Kraus, W M Cancer of the Spinal Cord, *Am J M Sc* **171** 825-836 (June) 1926

30 Becker, Gosta Liver Treatment in Diseases with a Blood Picture of Pernicious Anemia, *Acta med Scandinav*, supp 34, 1930, pp 70-74

31 Grinker, R R Pernicious Anemia, Achylia Gastrica and Combined Cord Degeneration and Their Relationship, *Arch Int Med* **38** 292-302 (Sept) 1926 Little, W D, Zerfas, L G, and Trusler, H M Chronic Obstruction of the Small Bowel The Result of Two Entero-Enterostomies and Apparently the Cause of Pernicious Anemia, *J A M A* **93** 1290-1291 (Oct 26) 1929 Meulengracht, E Pernicious Anemia in Intestinal Stricture (with One Liver-Treated Case), *Acta med Scandinav* **72** 231-240, 1929

32 Hurst, A F A Case of Addison's Anaemia with Subacute Combined Degeneration of the Spinal Cord and Normal Gastric Secretion Following Chronic Obstruction of the Ileum, *Guy's Hosp Rep* **83** 47-52 (Jan) 1933

33 Salus, Fritz Zur Entstehung der funikularen Myelitis, *Klin Wchnschr* **11** 237-240 (Feb 6) 1932

picture and signs of subacute combined degeneration of the spinal cord were noted, but the spinal cord was not examined at necropsy. We observed a woman aged 60 who had multiple intestinal fistulas and a fecal fistula following appendectomy, later, the hematologic and neurologic picture of pernicious anemia developed, and typical subacute combined degeneration was verified at necropsy.

Balo³⁴ described a case in which funicular myelitis was associated with obstruction at the papilla of Vater, degeneration in the tail of the pancreas, marked increase in the islands of Langerhans and some lymphocytic infiltration. The illustrations which were included might pass for those of advanced degeneration of the spinal cord in a case of pernicious anemia. Inconstant paresthesias, ataxic paraplegia, absence of the patellar and achilles tendon reflexes, the presence of the Babinski reflexes and loss of cutaneous sensibility below the distribution of the fourth lumbar segment were noted. Baló said there had been no signs of pernicious anemia, but he did not say how the presence of this condition had been excluded. In 1 of our cases, that of a man aged 36 who had been subjected to cholecystectomy elsewhere and had then vomited uncontrollably, a psychosis, objective evidence of peripheral multiple neuritis and flaccid paralysis of the sphincters developed. The value for the hemoglobin was 65 per cent, and there were 3,820,000 erythrocytes per cubic millimeter of blood. The results of gastric analysis were not recorded. The patient died after an illness of three months. Necropsy disclosed suppurating pancreatitis and marked degeneration of the peripheral nerves similar to that which occurs in cases of beriberi. An axonal type of reaction in the anterior horn cells and degeneration of the cells in the posterior root ganglions also were noted. There was no evidence of subacute combined degeneration.

The report of 2 cases by Dickey and McKinley³⁵ left no doubt that the clinical and pathologic picture of subacute combined degeneration of the type seen in pernicious anemia occurs in so-called prepernicious or preanemic pernicious anemia.

Neurologic changes commonly occur with pellagra, which is constantly being referred to as a cause of subacute combined degeneration of the spinal cord "like that seen with pernicious anemia," but one must be struck with the infrequency of the typical clinical or pathologic

34 Balo Josef. Myelitis funicularis als Folgeerscheinung der Erkrankung des Pankreas, *Deutsche Ztschr f Nervenhe* **102** 275-286, 1928.

35 Dickey, L. B., and McKinley, J. C. Subacute Combined Degeneration of the Spinal Cord Without Pernicious Anemia. Report of Two Cases with Autopsy Findings. *Journal-Lancet* **45** 331-334 (July 15) 1925.

picture of subacute combined degeneration in cases of pellagra Tucker ³⁶ reviewed the reports of 88 cases of pellagra in which there were neurologic findings In 6 of these cases necropsy was performed In an unpublished report we have reviewed 61 similar cases in 9 of which necropsy was performed Neither of these reviews disclosed any clinical or pathologic evidence of the characteristic type of subacute combined degeneration seen in pernicious anemia, although neurologic findings of various kinds were commonly encountered Some diffuse or focal degeneration of the fibers of the spinal cord has been reported in cases of pellagra,³⁷ but in only 1 case³⁸ were we able to find the familiar pathologic picture of subacute combined degeneration of the type seen in pernicious anemia, and in this report the results of gastric analysis and hematologic studies unfortunately had not been included A spinal cord which was said to have come from a patient who had died of pellagra was sent to us from an anatomic laboratory, and examination revealed changes typical of those encountered in cases of pernicious anemia Unfortunately, there was no clinical history in this case

In scurvy the problem is somewhat different from that in pellagra At least 1 of Nonne's²² alcoholic patients (case 6) had scurvy, but pernicious anemia can hardly be excluded Schlesinger³⁹ reported what appears to be a typical case in which the diagnosis was verified pathologically In this case subacute combined degeneration of the spinal cord and marked degeneration of the peripheral nerves were associated with war edema and scurvy, but unfortunately, neither the results of gastric analysis nor the results of studies of the blood were included

36 Tucker, B R The Neuropathology of Pellagra in Its Relation to the Cutaneous and Other Manifestations A Preliminary Report, South M J **28** 603-606 (July) 1935

37 Box, C R, Mott, F W, and Sambon, L W Pellagra in England An Account of Four Recent Cases, with a Description of the Histological Changes in the Nervous System with an Account of the History and Natural History of the Disease, Brit M J **2** 1-12 (July 5) 1913 Pentschew, A Ueber die Histopathologie des Zentralnervensystems bei der Psychosis pellagrosa, Ztschr f d ges Neurol u Psychiat **118** 17-48 1928 Spiller, W G, and Anderson, P V Pellagra with a Report of Two Cases with Necropsy, Am J M Sc **141** 94-106 (Jan) 1911 Winkelman, N W Beitrage zur Neurohistopathologie der Pellagra, Ztschr f d ges Neurol u Psychiat **102** 38-55, 1926

38 Guillain, G, Bertrand, I, Mollaret, P, and Lereboullet, J Etude anatomique d'un cas français de pellagre avec paraplegie, Bull et mem Soc méd d hop de Paris **50** 650-657 (May 11) 1934

39 Schlesinger, Hermann Erkrankungen des Nervensystems durch Nahrungsschaden und Hunger, Ztschr f d ges Neurol u Psychiat **59** 1-18, 1920

The cases reported by Wohlwill⁴⁰ and by Modes⁴¹ support the possibility that subacute combined degeneration of the type seen in pernicious anemia may be associated with scurvy, although pernicious anemia can hardly be said to have been excluded completely, even so far as this is possible, in these cases. The problem as it applies to spinae and allied conditions will be considered in detail later.

POISONING

The reactions of the nervous system to toxins differ considerably, but no case of poisoning could be found in which the clinical and pathologic pictures were indistinguishable from the neurologic picture seen in a case of well developed subacute combined degeneration of the type seen in pernicious anemia. In some of these cases, which have been well described by Davison and Keschner,⁴² the reaction manifests itself as a striking degeneration of the peripheral fibers of the spinal cord.

Tuczek's⁴³ contributions are usually cited to prove that changes in the spinal cord, like those which occur in cases of pernicious anemia, may result from poisoning with ergot. The neurologic symptoms in the cases reported by Tuczek included chiefly psychoses, epileptiform attacks, choreiform movements, vertigo, scanning speech, paresthesias, Romberg's sign and loss of patellar tendon reflexes. The pathologic picture in the spinal cord resembled that of tabes dorsalis rather than that of subacute combined degeneration.

In Filimonoff's⁴⁴ case of poisoning by *Lathyrus sativus* the poisoning was complicated by senility and lymphatic leukemia. The neurologic symptoms of lathyrism are chiefly dysuria and spasticity. This is one of the few instances in which necropsy has been performed in a case of lathyrism. The principal changes in the spinal cord included pial thickening, a non-neuronal type of degeneration of the pyramidal tracts, some degeneration of the cerebellar tracts and sclerosis of the

40 Wohlwill, Friedrich. Zum Kapitel der pathologisch-anatomischen Veränderungen des Gehirns und Rückenmarks bei perniciose Anämie und verwandten Affektionen. *Deutsche Ztschr f Nervenhe* **68-69** 438-480, 1921.

41 Modes, Ulrich. Zur Aetiologie der funikularen Spinalerkrankung, *Ztschr f d ges Neurol u Psychiat* **78** 291-299, 1922.

42 Davison, Charles and Keschner, Moses. Myelitic and Myelopathic Lesions. A Clinicopathologic Study. Toxic Myelopathy, *Arch Neurol & Psychiat* **29** 600-614 (March) 1933.

43 Tuczek, Franz. Ueber die Veränderungen im Centralnervensystem, speziell in den Hintersträngen des Rückenmarks, bei Ergotismus, *Arch f Psychiat* **13** 99-154 1882. Ueber die bleibenden Folgen des Ergotismus für das Centralnervensystem, *ibid* **18** 329-347 1887.

44 Filimonoff, I. N. Zur pathologisch-anatomischen Charakteristik des Lathyrismus. *Ztschr f d ges Neurol u Psychiat* **105** 76-92 1926.

vessels Filimonoff placed particular emphasis on the occurrence of the degeneration of the pyramidal tracts

An article by Oppenheim⁴⁵ often has been cited as proof that subacute combined degeneration, like the degeneration seen in pernicious anemia, may be caused by lead poisoning. The clinical diagnosis in the case which he reported had been multiple sclerosis. Necropsy revealed degeneration in Goll's tract, in the pyramidal tract, in the cerebellar tracts and in Clarke's column, an inflammatory reaction, an old infarction in the pons, and marked disease of the vessels. Oppenheim said he was undecided whether lead or syphilis was responsible for these changes and concluded that the lesions were certainly of vascular origin.

MISCELLANEOUS CAUSES

Günkel⁴¹ has said: "It is rare to see a severe secondary anemia patient with a red blood cell count as low as the usual pernicious anemia without the presence of tingling and numbness, which usually are not associated with cord degeneration. These paresthesias caused by any type of anemia should be attributed to changes in the peripheral nerves." Biemer, on the other hand, stated the opinion that funicular degeneration probably underlies the paresthesias of pernicious anemia. It should be emphasized that the typical paresthesias of pernicious anemia are continuous and cannot be "rubbed away." It is unsafe to disregard the degeneration of the nerves, which has been described by Hamilton and Nixon in cases of pernicious anemia as a possible source of the paresthesias in most instances, on the other hand, the frequency with which the same type of paresthesias ascend from the feet to encircle the lower part of the trunk to an indefinite level suggests that the changes in the spinal cord also may be capable of producing the paresthesias.

That secondary anemia alone causes persistent paresthesia or subacute combined degeneration of the spinal cord of the type seen in pernicious anemia can hardly be accepted as proved, clinical evidence alone seems to controvert this, as does the excellent study by Weil and Davison⁴⁶. Not infrequently they observed that what clinically looked like subacute combined degeneration of the spinal cord in cases of secondary anemia turned out to be something entirely different pathologically.

⁴⁵ Oppenheim, Hermann. Zur Lehre von der multiplen Sklerose, Berl klin Wchnschr **33** 184-189, 1896.

⁴⁶ Weil, Arthur, and Davison, Charles. Changes in the Spinal Cord in Anemia. A Clinicomicroscopic Study, Arch Neurol & Psychiat **22** 966-996 (Nov.) 1929.

Several cases in which amyotrophic lateral sclerosis was complicated by degeneration in the posterior funiculus have been described⁴⁷ In the case reported by Stone in which there was typical pernicious anemia associated with atrophy of the small muscles of the hands, pathologic study verified the expected picture In Hassin's report, in which there was no record of blood counts or gastric analysis, aseptic meningitis accompanied the amyotrophic lateral sclerosis He explained the combination as the result of activity of one toxin, and he made the pertinent remark that combined sclerosis does not mean subacute combined degeneration Viets,⁴⁸ in the discussion of Hassin's paper, emphasized the importance of insisting on good clinical evidence Schaller⁴⁹ noted, as we also have, that liver therapy does not seem to help in cases of amyotrophic lateral sclerosis

In many cases of infestation with *Bothriocephalus*⁵⁰ the typical clinical and pathologic picture of subacute combined degeneration of the type seen in pernicious anemia has been observed, yet one must be cautious in drawing the conclusion that this parasite is responsible for the typical lesion in the spinal cord, since proof consists of cure after removal of the parasite

Infestation with *Ancylostoma duodenale* also has been regarded as a cause of subacute combined degeneration,⁵¹ but the clinical picture in this case was unusual, and there was no report of a necropsy

According to Keschner and Davison,⁵² arteriosclerotic myelopathy is infrequent, it occurred only twice in 200 cases of cerebral arterio-

47 (a) Davison, Charles, and Wechsler, I S Amyotrophic Lateral Sclerosis with Involvement of Posterior Column and Sensory Disturbances A Clinicopathologic Study, *Arch Neurol & Psychiat* **35** 229-239 (Feb) 1936 (b) Hassin, G B Amyotrophic Lateral Sclerosis Complicated by Subacute Combined Degeneration of the Cord Clinical and Pathologic Report of a Case, *ibid* **29** 125-136 (Jan) 1933 (c) Holmes, Gordon A Case of Combined Degeneration of the Spinal Cord with Amyotrophy, *Rev Neurol & Psychiat* **11** 76-88, 1913 (d) Nonne, M Rückenmarksuntersuchungen in Fällen von pernicioaser Anämie, von Sepsis und von Senium, nebst Bemerkungen über Marchi-Veränderungen bei akute verlaufenden Rückenmarksprocessen, *Deutsche Ztschr f Nervenh* **14** 192-241, 1899 (e) Stone, T T Sub-Acute Combined Degeneration of the Spinal Cord with Chronic Changes in the Anterior Horns of the Cervico-Dorsal Region A Histopathological Study, *J Nerv & Ment Dis* **73** 41-54 (Jan) 1931

48 Viets, H R, in discussion on Hassin^{47b}

49 Schaller, Walter, in discussion on Hassin^{47b}

50 Naegeli Ueber perniziose Anämie, abstr, *Klin Wchnschr* **9** 1843-1844 (Sept 27) 1930

51 Early, P V Subacute Combined Degeneration of the Cord Associated with *Ankylostomum Duodenale* and Achlorhydria, *China M J* **40** 465-466 (May) 1926

52 Keschner, Moses, and Davison, Charles Myelitic and Myelopathic Lesions III Arteriosclerotic and Arteritic Myelopathy, *Arch Neurol & Psychiat* **29** 702-725 (April) 1933

sclerosis. It appears as a patchy gliosis. In 1 of our cases, that of a man aged 70, there had been constant tingling of the hands and feet for three weeks, marked weakness and incoordination. Vibratory sensibility was absent over the iliac crests and malleoli, all tendon reflexes were absent, and the sphincters were paralyzed. Necropsy revealed gliosis in the posterior column of the spinal cord, degeneration of the periphery of the spinal cord without ballooning of the fibers or gliosis, degeneration of the roots of the spinal nerves and arteriosclerosis. Myelopathic lesions which are the result of arteritis are much more frequent than those which are the result of arteriosclerosis. In all the cases reported by Keschner and Davison the glial response was poor. Some writers have said that arteriosclerotic changes are common in the spinal cord.

Nonne,^{47d} in a study of 10 senile patients, observed that the associated changes in the spinal cord did not evince themselves through any particular neurologic signs. In these 10 cases there was an increase of neuroglia, and there often was simple atrophy of nerve fibers in the periphery of the spinal cord, without inflammation and independent of sclerosis of the vessels. Diminution of vibratory sensibility is common among patients who are beyond the fifth decade of life, and this must be considered in deciding to what extent impairment in vibratory sensibility may be utilized in the diagnosis of subacute combined degeneration in cases of pernicious anemia. In 1 of our cases, that of a man aged 70 who had pernicious anemia and a loss of vibratory sensation over the iliac crests and the malleoli, necropsy disclosed marked thinning of the fibers of the anterior and posterior roots of the spinal nerves but did not disclose anything to suggest subacute combined degeneration of the spinal cord. According to Pearson,⁵³ impairment of vibratory sensibility among elderly persons is the result of arteriosclerotic circulatory impairment in the thoracic segment of Goll's tract.

Curschmann,⁵⁴ who had stated that he doubted the existence of subacute combined degeneration with anything but pernicious anemia, reversed his opinion on the basis of clinical findings, which were not altogether typical, in a case of hemolytic icterus. Necropsy was not performed in this case. Delbeke and Van Bogaert,⁵⁵ however, reported a case in which necropsy revealed changes in the spinal cord that were

53 Pearson, G. H. J. Effect of Age on Vibratory Sensibility, *Arch. Neurol. & Psychiat.* **20**: 482-496 (Sept.) 1928.

54 Curschmann, Hans. Ueber funikuläre Myelose bei hämolytischem Ikterus, *Deutsche Ztschr. f. Nervenheilk.* **122**: 119-125, 1931.

55 Delbeke, R., and Van Bogaert, L. Les myélites funiculaires en dehors de l'anémie pernicieuse. II. Une paraplégie à type de compression au cours d'un ictère hémolytique, *Ann. de méd.* **34**: 382-397 (Nov.) 1933.

like those noted in cases of pernicious anemia. The spinal fluid contained an increased amount of albumin and there was mild pleocytosis. The value for the hemoglobin in the blood was 70 per cent, and there were 2,900,000 erythrocytes per cubic millimeter of blood. The results of gastric analysis were not recorded.

Hemorrhagic and infiltrative lesions of the nervous system are fairly common in leukemia, occurring in 20.5 per cent of cases.⁵⁶ Such lesions are in keeping with this disease but that changes which are "just like those of pernicious anemia" should occur in the spinal cord in cases of leukemia is not altogether what might be expected. One of the other of Schultze's⁵⁷ contributions is usually quoted as authority for the occurrence of such lesions in cases of leukemia. The more recent reference is to a twelve line discussion in which Schultze referred to the earlier publication. In this admirably clear and concise article he described the occurrence of swollen and partly degenerated axis-cylinders, singly and in groups, three to twenty to the cross-section, in all columns of the spinal cord, especially in the lateral columns. These changes, he said, may be seen also in cases of nephritis, being observed near the periphery of the lateral columns. There was no trace of leukocytic or hemorrhagic infiltration.

Pernicious anemia of pregnancy seems to offer a hopeful field for the discovery of a typical example of subacute combined degeneration, like that which occurs in cases of pernicious anemia. Naegeli said that glossitis, achylia and degeneration of the spinal cord do occur in cases of pernicious anemia of pregnancy, but Filo⁵⁸ said that neurologic changes are rare in such cases. The time factor may not permit the complete development of subacute combined degeneration. Myelitis of pregnancy⁵⁹ must not be confused with subacute combined degeneration although in cases of myelitis the history may be strongly suggestive of typical combined degeneration of the spinal cord.⁶⁰ Hassin and Ettleson⁶¹ gave an excellent description of the pathologic changes

56 Schwab, R. S., and Weiss, Soma. The Neurologic Aspect of Leukemia, *Am J M Sc* **189** 766-778 (June) 1935.

57 Schultze, Friedrich. I. Ueber das Vorkommen gequollener Axencylinder im Rückenmarke, *Neurol Centralbl* **3** 193-195 (May) 1884, Historische Notiz über Degenerationsherde in der weissen Substanz bei Leukämie und über Degenerationen im Rückenmark bei Zehrkrankheiten, *Deutsche Ztschr f Nervenhe* **11** 162-163, 1897.

58 Filo, Emanuel. Ueber die Schwangerschaftsperniziosa, *Folia haemat* **44** 446-474, 1931.

59 Rosenberg, F., and Schmincke, A. Zur Pathologie der toxischen Graviditätsmyelitis, *Virchows Arch f path Anat* **184** 329-345, 1906.

60 Spitzer, Walther. Myelitis und Rückenmarksläsion in ihren Beziehungen zu Schwangerschaft und Geburt, *Arch f Gynäk* **152** 517-528, 1933.

61 Hassin, G. B. and Ettleson, Abraham. Paraplegia of Pregnancy (Subacute Combined Degeneration of the Cord), *Arch Neurol & Psychiat* **32** 1273-1281 (Dec.) 1934.

that occurred in a case in which they classified the disorder as due to subacute combined degeneration of the spinal cord associated with pregnancy. The authors said that the changes noted "were degenerative, of the type observed in subacute combined degeneration of the spinal cord, they resembled nothing else." Unfortunately, in this case the subacute combined degeneration was not uncomplicated. The patient was a girl aged 19 years who had had gonorrhea and syphilis. Paraplegia and urinary incontinence had occurred three days after an attack of pharyngitis, later blood culture revealed the presence of staphylococci. Necropsy disclosed multiple abscesses of the viscera and marked degeneration of the lateral columns of the spinal cord. The degeneration was less marked in the anterior columns than it was in the lateral columns, and the degenerative changes were slight in the posterior columns. There was axonal degeneration of the ganglion cells, and the blood vessels and meninges were markedly infiltrated with lymphocytes and polymorphonuclear leukocytes. In another case, which was reported by Hassin and Stone,⁶² the illness began two weeks post partum. The symptoms become progressively worse, three years after the onset of the illness the lower extremities became markedly adducted and flexed. Examination revealed complete spinal subarachnoid block. Laminectomy was performed, and a large blood clot was removed. Necropsy was limited to a part of the cord. The results of gastric analysis were not mentioned.

Kahler and Pick⁶³ gave one of the earliest descriptions of subacute combined degeneration, probably of the so-called primary type. In 1 of our cases in which the disability began early in childhood and was progressive, the combined sclerosis was marked by complete absence of any sieve-like appearance in the spinal cord and by an extraordinarily dense net work of glial fibers.

A number of unclassified diseases remain in which subacute combined degeneration has been mentioned as a complication of interest. Anemia was said to have been absent in a case⁶⁴ in which the disease clinically and pathologically resembled the subacute combined degeneration of pernicious anemia. The value for hemoglobin was 80 per cent, and there were 3 600 000 erythrocytes per cubic millimeter of blood. Examination of blood smears did not reveal any abnormality. The patient had had attacks of diarrhea. The results of gastric analysis

62 Hassin, G. B. and Stone, T. T. Subacute Combined Degeneration of the Spinal Cord. Report of a Case Following Childbirth and Complicated by Spinal Epidural Hemorrhage, *Arch Neurol & Psychiat* **34** 401-406 (Aug.) 1935.

63 Kahler, Otto, and Pick, Arnold. Ueber kombinierte Systemerkrankungen des Rückenmarkes, *Arch f Psychiat* **8** 251-282, 1878.

64 Schaeffer, Henri and Vialard. Sclerose combinee subaigue de la moelle sans anemie, *Paris med* **2** 301-305 (Oct 5) 1929.

were not reported. In another case,⁶⁵ which was reported as a case of subacute combined sclerosis without anemia or cachexia, the signs pointed to involvement of the posterior columns and the extrapyramidal system, however, the rigidity was interpreted as originating in the pyramidal tracts. Free hydrochloric acid was absent from the gastric juice, there was no necropsy.

Delhayé and Van Bogaert⁶⁶ reported a case of subacute combined degeneration associated with widespread cellular changes in the nervous system. The patient was a man aged 60 who was deaf and had sphincter disturbances. Babinski reflexes were present. The skin was bronzed, and the patient was emaciated. The value for the hemoglobin was 90 per cent, and there were 3,300,000 erythrocytes per cubic millimeter of blood. There were some myelocytes in the blood. In addition to the changes in the spinal cord, necropsy revealed arteriosclerosis, enlargement of the liver and spleen, perivascular lymphocytic infiltration of the skin, periportal cirrhosis, cortical sclerosis of the adrenal glands, hyperplasia of other parts of the chromaffin system and some changes in the hypophysis cerebri. The disease was classified as a mixed endocrine disorder with lesions in the adrenal glands, the afferent chromaffin system and the hypophysis cerebri.

In the unusual case reported by Sjogren and Wohlfahrt⁶⁷ both the clinical and the neuropathologic picture were those of subacute combined degeneration of the type seen in pernicious anemia. The patient was cachectic, and Bence-Jones' protein was present in the urine. The value for hemoglobin was 67 per cent, and there were 2,900,000 erythrocytes per cubic millimeter of blood. The results of gastric analysis were not recorded, and the diagnosis remained in doubt.

Bodechtel,⁶⁸ in his excellent article on funicular spinal disease, showed sections of the spinal cord, in at least four illustrations the changes strongly resembled those of pernicious anemia. The author simply said that these spinal cords were not from patients with pernicious anemia, he did not give any further data. In another case of subacute combined degeneration the presence of dementia paralytica had not been suspected until the blood and sections of the brain were studied.

65 Thomas, Andre, Schaeffer, H., and Amyot, R. Sclerose combinee subaiguë de la moelle sans anemie, in cachexie, *Rev. neurol.* **2** 561-567 (Nov.) 1929.

66 Delhayé, A., and Van Bogaert, L. Les myelites funiculaires en dehors de l'anémie pernicieuse. I. Une paraplegie en flexion au cours d'un syndrome endocrinien et hépatique avec mélanopigmentation, *Ann. de med.* **34** 42-68 (June) 1933.

67 Sjogren, V. H., and Wohlfahrt, S. Ein Symptomenkomplex, funikuläre Spinalerkrankung sowie Bence Jones' Eiweisskörper im Harn. I. Klinische und anatomische Befunde, *Acta psychiat. et neurol.* **8** 253-260, 1933.

68 Bodechtel, G. Zur Histopathologie der funikulären Spinalerkrankung mit besonderer Berücksichtigung der bei der perniciosen Anämie zu sehenden Grosshirnveränderungen, *Ztschr. f. d. ges. Neurol. u. Psychiat.* **137** 104-167, 1931.

The funiculi of the spinal cord may be altered by many diseases and in many ways. The differential diagnosis cannot always be made on clinical evidence alone. Before the cause of subacute combined degeneration of the spinal cord like that which occurs in cases of pernicious anemia can rightly be determined, typical and well developed clinical and pathologic signs and symptoms must be brought forward as evidence. On the basis of a survey of the important available literature, it appears that this familiar and challenging picture may be brought about by chronic alcoholism, gastric carcinoma, obstruction and fistulas of the intestinal tract, pernicious anemia, so-called prepernicious anemia and scurvy (this may have been a complication). It possibly may be similarly related to pancreatitis, pellagra and hemolytic icterus, and it has been in some manner associated with amyotrophic lateral sclerosis and a number of unclassified diseases.

An important physiologic principle appears to be involved. Careful hematologic studies, gastric analysis and an investigation of the presence of Castle's intrinsic factor, if facilities are available, possibly would lead to the disclosure of some one underlying cause, probably nutritional and in the nature of a deficiency.

A CLINICAL REVIEW OF CASES IN WHICH A DIAGNOSIS OF COMBINED SCLEROSIS WAS MADE

In reviewing our group of approximately 2,000 cases in which the disease was classified as subacute combined degeneration of the spinal cord, we excluded all cases in which gastric analysis revealed absence of free hydrochloric acid (fig 1). Thus most, if not all, cases of pernicious anemia were eliminated. The insert, for purpose of comparison, represents the findings noted in pernicious anemia, expressed in percentage of cases. We should like to draw attention to the frequency of the paresthesias and to the relative prominence of involvement of the posterior columns as compared with involvement of the lateral columns and to suggest a comparison of the entire insert with other figures in the illustration.

In the first group of cases we classified the combined sclerosis rightly or wrongly as arteriosclerotic or senile. In this group of cases the paresthesias were usually transitory and otherwise not typical of those seen with pernicious anemia. Complications of various kinds, as might be expected among patients of the same age, were common but could not safely be regarded as causes.

In the group in which the diagnosis was questionable there was usually a suggestion of trauma, infection or multiple sclerosis, but the objective findings were those of combined involvement. In the case which was said to illustrate the type of degeneration seen in pernicious

anemia, the diagnosis was complicated by the possibility of superimposed arsenical neuritis and by predominant unilateral spasticity. In 1 case in this group there was an obstruction in the first part of the duodenum and Korsakoff's psychosis, in another case myxedema and in another postural hypotension. Several of the cases in this group might have been included in the group of cases in which arteriosclerosis was present.

We do not mean to imply that subacute combined degeneration and multiple sclerosis are in any way related, but the differential diagnosis

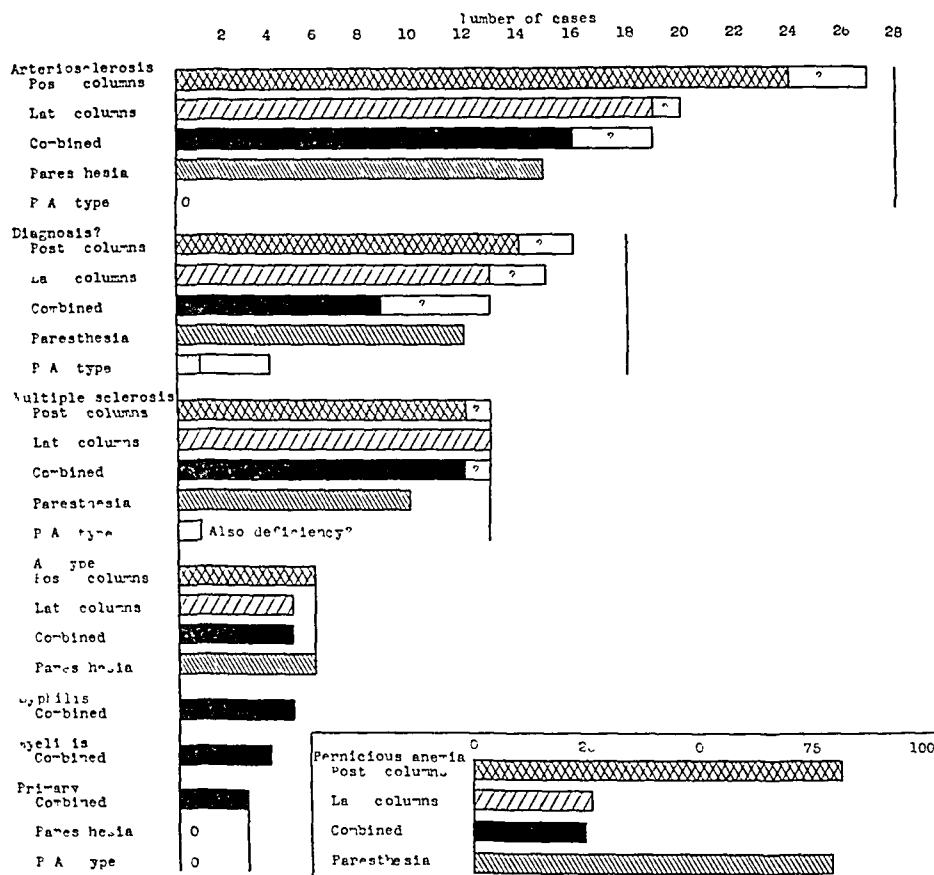


Fig 1—Groups of cases in which there were signs of involvement of the posterior and lateral columns of the spinal cord. Post indicates posterior, Lat, lateral, P A, pernicious anemia.

may be difficult in early stages. In 1 case we classified the condition as combined sclerosis associated with severe and chronic infection of the nasal sinuses after examination in 1922. Seven years later necropsy disclosed typical multiple sclerosis. In 1 of the cases of multiple sclerosis the history of diarrhea, vomiting and "sore mouth" suggested an associated dietary deficiency. The diagnosis of multiple sclerosis in the cases in this group was determined largely on the basis of the previous or subsequent history or on the basis of findings obtained by examination of the spinal fluid.

There were 6 cases of subacute combined degeneration of the type seen in pernicious anemia which, in view of the presence of free hydrochloric acid in the gastric juice, we could not classify as cases of pernicious anemia. Fortunately, we made lumbar punctures in 2 of these cases, but unfortunately this was not done in the other cases. Examination of the spinal fluid suggested the possibility of meningo-radiculomyelitis in 1 case and multiple sclerosis in the other. In the first case "stomach trouble" had been present for fifteen years, and roentgenologic examination revealed the presence of a duodenal ulcer. In the third case the patient became depressed after the death of his wife, refused to eat and lost 50 pounds (22.7 Kg.) but improved promptly as a result of liver therapy. He had also postural hypotension which is not infrequently associated with neurologic signs suggestive of subacute combined degeneration or multiple sclerosis. In the fourth case there was associated glossitis. The fifth case was that of a man aged 49 who, according to his physician, "became rigid as a board before he died." The physician of the sixth patient informed us seven years after we had seen the patient that the value for hemoglobin was 82 per cent, that there were 3,610,000 erythrocytes per cubic millimeter of blood and that macrocytes occasionally were noted in blood smears. The patient had been taking liver since she left the clinic, with the exception of the eight months that preceded the writing of the physician's letter. Her neurologic condition had become only slightly worse than it had been.

A case not included in this group illustrates the value of lumbar puncture when the diagnosis is doubtful.

The patient was a physician aged 62. Five months before he came to the clinic persistent tingling had developed in his feet, which had also become somewhat ataxic. There had not been any paresthesia of the fingers. Objective examination disclosed a moderate impairment of vibratory sensibility over the malleoli, absence of vibratory sensibility over the iliac crests, slight impairment of superficial and postural sensibility in the toes and slight Babinski reflexes. The tentative diagnosis was subacute combined degeneration of the spinal cord, but the hematologic picture was entirely normal, and free hydrochloric acid was present in the stomach. Lumbar puncture disclosed complete spinal subarachnoid block by jugular compression tests; there was 110 mg. of protein per hundred cubic centimeters of spinal fluid. Iodized poppy-seed oil 40 per cent was injected into the spinal canal for the purpose of localization. Exploration revealed dense adhesive arachnoiditis at the level of the eleventh thoracic vertebra. Only then did the patient recall that while he had been casting for trout some months before the onset of his disability he had fallen 20 feet (6 meters) down a bank and had injured his back.

In the cases of syphilis, myelitis and primary degeneration of the central nervous system there was no evidence of subacute combined degeneration of the type seen in pernicious anemia.

To summarize, we have observed 77 cases in which there were signs of involvement of the posterior and lateral columns of the spinal cord and in which free hydrochloric acid was present in the gastric contents. The latter finding practically eliminates pernicious anemia as a cause of the involvement. When we add gradually developing, symmetrical, persistent paresthesias of the hands and feet, the clinical neurologic picture becomes that seen typically in cases of pernicious anemia. There were 8 cases in which these symptoms were present, in 3 of these there was no reason for believing that a nutritional factor entered into the cause, in the remaining 5 there was reason for thinking so, although we do not venture to say that the pathologic examination in these cases would have disclosed classic subacute combined degeneration of the spinal cord. To borrow a term from the serologic laboratory, occasional "false positive results," which are indistinguishable clinically at a given time from the picture typically seen with pernicious anemia, may be met. In cases in which the diagnosis is doubtful an examination of the spinal fluid increases the accuracy of the diagnosis. In none of these could the exact pathologic nature of the lesion in the cord be verified.

SPRUE AND ALLIED CONDITIONS

Sprue and allied conditions deserve special attention. In a review of more than two hundred available articles on the subject of sprue it was found that only twenty included evidence of organic involvement of the nervous system (table 2) ⁶⁹

69 (a) Baumgartner, E. A., and Thomas, W. S. A Case of Tropical Sprue with Autopsy, *Clifton M. Bull.* **11** 90-93, 1925. (b) Elders, C. Tropical Sprue and Pernicious Anaemia. Aetiology and Treatment, *Lancet* **1** 75-77 (Jan 10) 1925. (c) Reed, A. C., and Wyckoff, H. A. The Common Picture of Sprue, Pernicious Anemia, and Combined Degeneration, *Am J Trop Med* **6** 221-237 (May) 1926. (d) Baumgartner, E. A., and Smith, G. D. Pernicious Anemia and Tropical Sprue, *Arch Int Med* **40** 203-215 (Aug) 1927. (e) Holst, J. E. Ein in Danemark aufgetretener Fall von Sprue, *Acta med Scandinav* **66** 74-99, 1927. (f) Graves, M. L., in discussion on Wood ^{72b}. (g) Korsberg, Axel quoted by Holst ^{69e}. (h) Bröns, J., quoted by Holst ^{69e}. (i) Low, G. C., and Benton, D. Sprue in Natives, *J Trop Med* **30** 193 (Aug 2) 1927. (j) Reed, A. C., and Ash, J. E. Atypical Sprue, *Arch Int Med* **40** 786-799 (Dec) 1927. (k) Baumgartner, E. A. Parathyroid in the Treatment of Tropical Sprue, *Am J Trop Med* **7** 181-191 (May) 1927. (l) Antoine, Edouard. Trois cas de diarrhée grave à allure de sprue, étude de cette affection tropicale, *Arch d mal de l'app digestif* **18** 45-65 (Jan) 1928. (m) Richardson, Wyman, and Klumpp, T. G. Sprue. Report of a Case Treated with the Authorized Liver Extract Effective in Pernicious Anemia, *New England J Med* **199** 215-218 (Aug 2) 1928. (n) Thaysen, T. E. H. Diskussion. Die Symptomatologie der nicht tropischen Sprue, *Verhandl d Gesellsch f Verdauungs- u Stoffwechselkr* **8** 152-155, 1928. (o) Zadek, Ernst. Ueber Sprue, *Med Klin* **24** 776-777 (Mar 18) 1928. (p)

Ashford^{69r} gave an excellent summary of the general clinical picture. Regarding the symptoms which are referable to the spinal cord he said:

This syndrome is extremely rare in sprue. With exceptions noted, numbness in the extremities and tetanoid cramps in muscles of leg (half of the writer's cases and otherwise explained), the symptoms relative to cord lesions are not characteristic of sprue.

Insomnia, sluggish or abolished knee reflexes, nervous depression and irritability, vague muscle pains, palpitation of the heart, loss of memory, and weight over the cerebellum are frequent in the latter disease, but headache and dizziness are not common. That the central nervous system is not organically affected, as a rule, and that these symptoms are functional due to disordered nutrition is seen in their prompt dissipation by an adequate sprue diet, perhaps reenforced by calcium therapy and parathyroid extract subcutaneously administered. Only rarely are definite lesions of the cord evidenced in sprue and then they are almost always slight and ephemeral when a proper diet is applied.

Fauley⁷⁰ said: "I have never observed subacute combined degeneration in sprue, though neuritic manifestations are common enough."

The mental state in cases of sprue is usually one of depression.⁷¹ The patient reported on by Suarez lost his ideas of persecution and

Holmes, W. H., and Starr, Paul. A Nutritional Disturbance in Adults Resembling Celiac Disease and Sprue, Emaciation, Anemia, Tetany, Chronic Diarrhea and Malabsorption of Fat, *J. A. M. A.* **92** 975-980 (March 23) 1929. (q) Hance, J. B. Notes on the Pathogenesis of Sprue and the Asthenic Diarrhoea of Indians, with Special Reference to the Rôle Played Therein by Amoebiasis. The Probable Identity of the Two Former Conditions, and Their Connection with Addisonian Anaemia—Subacute Combined Degeneration of the Cord—Hunterian Glossitis Syndrome of Hurst, *Indian M. Gaz.* **65** 125-130 (March) 1930. (r) Ashford, B. K. The Differential Diagnosis of Sprue and Pernicious Anemia, *Am. J. Trop. Med.* **12** 199-215 (May) 1932. (s) Keefer, C. S., Yang, C. S., and Huang, K. K. Anemia Associated with Chronic Dysentery. Clinical Considerations, with Special Reference to the Cause and Treatment, *Arch. Int. Med.* **47** 436-466 (March) 1931. (t) Suarez, Jenaro. Pernicious Anemia and Sprue, *Porto Rico J. Pub. Health & Trop. Med.* **7** 145-165 (Dec.) 1931. (u) Brown, Madeline R. The Pathology of the Gastro-Intestinal Tract in Pernicious Anemia and Subacute Combined Degeneration of the Spinal Cord. Study of One Hundred and Fifty-One Autopsies, *New England J. Med.* **210** 473-477 (March 1) 1934. (v) Thaysen, T. E. H. La steatorrhee idiopathique, la sprue tropicale et non tropicale et l'infantilisme intestinal, *Arch. d. mal. de l'app. digestif* **24** 123-169 (Feb.) 1934. (w) Castle, W. B., Rhoads, C. P., Lawson, H. A., and Payne, G. C. Etiology and Treatment of Sprue. Observations on Patients in Puerto Rico and Subsequent Experiments on Animals, *Arch. Int. Med.* **56** 627-699 (Oct.) 1935.

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71 Ashford, B. K. A Case of Hypoplastic Anemia, Pernicious Type, in the Course of Sprue, with Frequently Repeated Hematological Examinations, *Porto Rico J. Pub. Health & Trop. Med.* **7** 11-22 (Sept.) 1931. Baumgartner and Smith^{69d} Campbell, R. D. Sprue in Southwest Virginia. A Case Report. *Virginia M. Monthly* **58** 380-382 (Sept.) 1931. Malcolmson, G. E., and Murphy, K. N. The Frequency of Sprue Among Indians in Madras, *Indian M. Gaz.* **66** 192-193 (April) 1931.

TABLE 2.—Principal Neurologic Features Noted in Cases of Spine and Allied Conditions Reported

Year	Author	Paresthesia			Reflexes		Sensation		Comments
		Hands	Feet	Patellar	Achilles Clonus	Babinski	Vibra- tion	Joint	
1925	Baumgartner and Thomas ^{60a}	+	+	Diminished, grade 2					Question of slight degeneration of cervical portion of spinal cord at necropsy
1925	Filders ^{60b}								Ataxia, anesthesia of legs
1926	Reed and Wyckoff ^{60c}	+	+	Absent	Absent				Clumsiness of hands
1926	Reed and Wyckoff	+	+						
1927	Baumgartner and Smith ^{60d}	Normal	Normal	Increased	+	+			Numbness and tingling in 8 to 15 cases
1927	Holst ^{60e}								Spastic paraplegia
1927	Graves ^{60f}								Patient 9 years of age, epileptoid syndrome
	Korsberg ^{60g}			Absent					Paresis of legs and sphincters
	Bröns ^{60h}			Absent					Polyneuritis
1927	Low and Benton ⁶⁰ⁱ		+	Absent					Irritability
1927	Reed and Ash ^{60j} (case 1)	+	+						Negative results of necropsy
1927	Reed and Ash (case 3)?	+	+						No free hydrochloric acid in stomach, necropsy revealed combined degeneration
	Reed and Ash (case 4)?								No free hydrochloric acid in stomach marked combined sclerosis, necropsy revealed combined degeneration
	Reed and Ash (case 5)?								Neuritis of both brachial plexuses, no test meal given
1927	Baumgartner ^{60k}			Absent					Left patellar reflex normal
1928	Antoine ^{60l} (case 3)	+	+	Absent					Transitory paresthesias, slight ataxia
1928	Richardson and Klumpp ^{60m}	+	+	Absent		±			Two cases, one patient could scarcely walk
1928	Thayson ⁶⁰ⁿ			Absent					
1928	Zadek ^{60o}			Absent					
1929	Holmes and Starr ^{60p} (case 2)	+	+						Total of 26 cases 20 of sprue, 3 of combined degeneration, 3 of pernicious anemia, 3 with paresthesia 2 with ataxia (groups not stated)
1929	Holmes and Starr (case 5)								Loss of memory, despondency
1930	Hance ^{60q}								Ataxia
1931	Ashford ^{60r} (case 39)		+	Absent					Peripheral neuritis
1931	Keefe, Yang and Huang ^{60s}			Absent					Combined degeneration
1931	Keefe, Yang and Huang			Absent					All reflexes?
1931	Szarev ^{60t} (case 21320)			Absent					One patient had free hydrochloric acid in stomach, pernicious anemia; degeneration of cord (necropsy report)
1934	Brown ^{60u}								Patient disappeared
1934	Thayson ^{60v}	±	±	Decreased in 3 cases		+			Total of 92 cases changes in central nervous system in 8 in 3 of 8 cases gas free acidity not reported, in 3, no free hydrochloric acid in stomach in 2 acid was found, disturbance of locomotion
1935	Cattle, Rhoads, Lawson and Payne ^{60w}	±	±						

hallucinations after treatment with liver had been instituted. Epileptoid and epileptiform convulsions and petit mal also have been observed.⁷²

Gastric analysis revealed the presence of free hydrochloric acid in 52 of the 93 cases of sprue and related conditions which have been observed at the clinic. The presence of free hydrochloric acid was regarded as presumptive evidence that no cases of pernicious anemia were included in this study. Neurologic examination was performed in 29 of the 52 cases.

The findings in 11 of these 29 cases are shown in table 3. In 6 of these cases there had been continuous paresthesias of the hands and

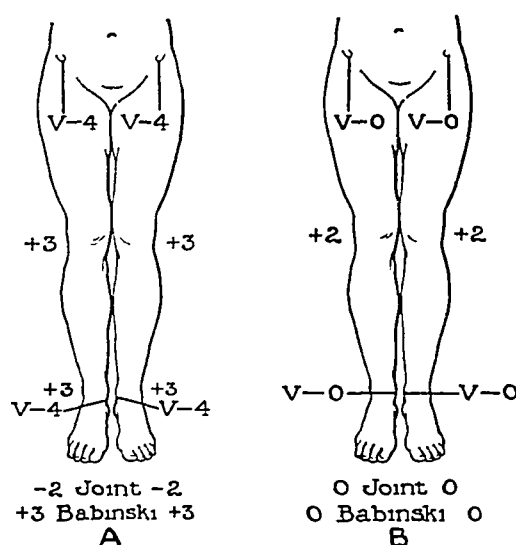


Fig. 2—Nontropical sprue in a man aged 26. Subacute combined degeneration of the spinal cord with improvement resulting from intramuscular injection of liver extract. *A*, March 6, 1934. For ten years the patient had had remitting attacks of watery diarrhea, abdominal pain, gas and bloating. Glossitis was noted two years previously. Paresthesia of the hands had been present for two months and paresthesia of the feet for one and one-half months. Astereognosis had developed. A histamine meal test showed free hydrochloric acid of 86. Hemoglobin, 10.4 Gm; erythrocytes, 2,580,000; macrocytic hyperchromic morphologic picture. On April 16, 1934, the paresthesia was improved. Vibration, —2, joint sensibility, —1, Babinski reflex, +2. On July 10, 1934, there was transitory paresthesia of the fingers. Vibration over the iliac crests, 0, over the malleoli, —2, joint sensibility, 0, Babinski reflex, +1, hemoglobin, 12.9 Gm; erythrocytes, 4,320,000, normal morphologic picture, absence of usual markings of small intestine, hypomotility. On July 8, 1935, hemoglobin, 10.5 Gm; erythrocytes, 3,960,000, moderate hypochromic, normocytic blood picture. *B*, April 22, 1936, general health only fair, some diarrhea, no glossitis, normal reaction of pupils to light, no injection of liver extract for past five months.

72 (a) Ashford, B. K. The Relation of Monilia Psilosis to Tropical Sprue and an Evaluation of Fermentation of Sugar as a Criterion for Specificity, *Porto Rico J. Pub. Health and Trop. Med.* **6**: 310-333 (March) 1931. (b) Wood, E. J. The Recognition of Tropical Sprue in the United States, *J. A. M. A.* **73**: 165-167 (July 19) 1919. (c) Holst.^{69e}

feet, in 6 cases the tendon reflexes were diminished or absent and in 1 case they were increased in 10 cases vibratory sensibility was impaired or absent, usually at both iliac crests and at the malleoli Macrocytosis was present in 8 cases We regard the neurologic condition in case 12 as a complication not directly related to sprue

Case 7 is of sufficient significance to warrant a more detailed report (fig 2)

TABLE 3—Summary of Data in Twelve Cases of Sprue and Related Conditions in Which Neurologic Examination Was Performed and Free Hydrochloric Acid Was Present

Case	Sex	Age, Years	Residence	Paresthesia*		Reflexes, Graded†			Sensation‡		Hydrochloric Acid in Gastric Juice§	Macrocytosis
				H iliacs	Feet	Patellar	Achilles Tendon	Babinski	Vibratory	Joint		
1	M	52	Indiana						0 —3		16	0
2§	M	63	North India	6	4				—4 —4		22	+
3	F	53	Manila	12	12				0 —3 —4	—2	66	+
4	M	65	Kentucky						0 —2		50	+
5	M	44	Illinois			—4					58	0
6	M	44	Washington	12	60	—4	—4		0 —2 —3	—2	38	+
7	M	26	Nebraska	2	1½	+3	+3	+3	—4 —4	—2	86	+
8	M	54	Illinois	36	36	—2	—4	+1¶	0 —2		34	+
9	M	56	Central America			—4	—4		—2 —2		10	+
10	M	43	Illinois	42	42	—4	—4		—4 —4	—2	18	0
11	M	54	West Indies				—2		—4 —4		20	+
12	M	30	Ohio			Palsy of left peroneal nerve					24	0

* Duration in months transitory paresthesia not included

† 0 represents normal Normal responses are not charted except under vibration, when upper figure represents vibratory sensation over crests of ilium and lower figure represents vibratory sensation over malleoli, —4 indicates absence of reflex

‡ Determined according to method of Topfer

§ Rectal sphincter, —2

|| Paresis of hands and feet, +3

¶ Presumably the palsy was caused by pressure and was not specifically related to nontropical sprue

A Jew aged 26 first came to the clinic on March 3, 1934 While in high school he had gone through about twelve periods of weakness, anorexia, loss of weight, pallor and vague abdominal distress These attacks had not caused him to miss school He entered college at the age of 17, when he again had gastrointestinal symptoms of the same type There were periods of constipation alternating with periods of diarrhea The stools were loose and watery but did not contain mucus or blood Because of these symptoms he was forced to dis-

continue college for two and a half years. During this period his appendix and tonsils were removed. In 1929 he returned to college, continued his work for three years and was graduated with honors. The symptoms had returned but, in addition, he had diarrhea and a sore mouth. Orange juice had been taken faithfully. After he completed his college work he never was strong enough to do much work. During the winter previous to his admission to the clinic the gastro-intestinal disturbance returned. Two months before he came to the clinic, tingling developed in the fingers, this spread and gradually involved the whole hand. He was unable to take money out of his pocket and had difficulty in buttoning his clothes because of this disturbance. Shortly after the onset of paresthesia in the fingers, tingling developed in the toes. He became irritable and depressed. His best weight had been 115 pounds (52.6 Kg.) when he was fully dressed, he weighed only 90 pounds (40.8 Kg.) when he came to the clinic.

General physical examination revealed a marked loss of weight, pallor, a smooth tongue, some reddened areas on the gums and some clubbing of the fingers. Moderate edema was present in the lower extremities. The essential laboratory findings were as follows. The concentration of hemoglobin was 10.3 Gm per hundred cubic centimeters of blood. The erythrocytes numbered 2,580,000 and the leukocytes 2,700 per cubic millimeter of blood. A differential blood count revealed that there were 30 per cent lymphocytes, 65 per cent monocytes and 63.5 per cent polymorphonuclear neutrophils. Morphologic examination of the blood smears showed marked macrocytosis and revealed that the erythrocytes were well filled with hemoglobin. There was little increased lobulation of the nucleus in the polymorphonuclear neutrophils. Howell-Jolly bodies and basophilic stippling were present. Gastric analysis after ingestion of ordinary cookie meal revealed that the value for the total gastric acidity was 38 and that for the free hydrochloric acid was 22, according to the method of Topfer. After the injection of histamine, values as high as 86 were obtained for free hydrochloric acid. The function of the liver was normal, as determined by the dye retention test. The volume index was 122. Roentgenoscopic examination of the small bowel showed some dilatation and hypomotility. The percentage of reticulated erythrocytes was from 1 to 2 before the institution of treatment. On March 11 a high calorie-high vitamin diet which was low in fat was prescribed, and in addition the patient was given five successive injections of 3 cc of liver extract. Weekly injections of liver extract were given thereafter. On March 18 the percentage of reticulated erythrocytes was 11.8. The patient had gained markedly in weight and strength, and when he was seen again, on July 9, the concentration of hemoglobin was 12.9 Gm per hundred cubic centimeters of blood and the erythrocytes numbered 4,320,000 and the leukocytes 5,100 per cubic millimeter of blood. Morphologically, the erythrocytes were normal in appearance.

The patient was again seen in July 1935, because of a recurrence of symptoms. At this time the concentration of hemoglobin was 10.5 Gm per hundred cubic centimeters of blood, the erythrocyte count was 3,960,000 and the leukocyte count was 3,500. No macrocytosis could be demonstrated. There was moderate hypochromasia in the erythrocytes. At this time, in addition to the liver extract, he was given 1 Gm of iron daily in the form of ferrous carbonate.

The outstanding neurologic findings on March 6, 1934, included diminution of the pupillary response to light. The reaction to convergence was normal. The patellar and achilles tendon reflexes were disproportionately active. The abdominal reflexes were absent. The Babinski, Chaddock, Rossolimo and Mendel-Bechterew reflexes were strongly pathologic bilaterally. There was definite inco-

ordination of the upper extremities, as tested with the finger to nose test. A moderate grade of astereognosis was present. Vibratory sensibility was absent over the iliac crest and lower extremities. Appreciation of movement of the joints was markedly impaired in the toes. There was slight disturbance of tactile sensibility over the toes. The diagnosis was subacute combined degeneration of the spinal cord associated with degeneration of the peripheral nerves. The neurologic examination was repeated on April 16, after the patient had undergone treatment for one month. He said he felt little better than he had at the time of the previous neurologic examination. The findings were essentially the same as they had been before, except that the Babinski and Chaddock reflexes were less marked than they had been previously. The Rosolimo and Mendel-Bechterew reflexes were no longer obtainable. Vibratory sensibility had improved somewhat, and the patient was able to feel the vibrations of the fork moderately well when it was placed over the iliac crest. The vibration could not be felt when the fork was placed over the malleoli of the right lower extremity, and vibratory sensation was moderately impaired when the fork was placed over the malleoli of the left lower extremity. Joint sensibility of the toes was only slightly impaired. Paresthesia of the hands and feet had diminished, and the patient was able to write with greater facility, to tie his necktie and button his clothes better than previously. Objectively there was decided improvement.

Another neurologic examination was carried out on July 10. The pupils remained rather small and somewhat irregular, reaction to light was somewhat impaired. The achilles tendon reflexes were still relatively active. The Babinski and Chaddock reflexes were still slightly pathologic. Appreciation of vibratory sensibility was normal over the iliac crests and only slightly impaired over the malleoli. The tingling had practically disappeared from the fingers and toes and was present only at times in the fingers of the right hand, particularly, and in the second and third digits of the left hand. The patient no longer complained of stiffness and awkwardness of the extremities. There was great improvement in his general strength, and he had no difficulty in walking, even in the dark. Subjectively and objectively there had been great improvement.

Reexamination on April 22, 1936, revealed that the right pupil was somewhat larger than the left, both pupils reacted normally to light and in convergence. The tendon reflexes were still more active than normal. The Babinski reflex was now normal. Vibratory and joint sensibility were normal, as was stereognosis. The general health of the patient was only fair. Some diarrhea was present, but there had been no glossitis. Because of economic conditions he had not received intramuscular injections of liver extract for five months. It is likely that the omission of liver extract had been responsible in part for the return of some symptoms.

The important neurologic findings which may occasionally be observed with sprue, nontropical sprue and idiopathic steatorrhea and which are dependent on organic involvement of the nervous system usually express themselves as persistent acroparesthesias, depression of the tendon reflexes, especially those of the lower extremities, impairment of vibratory sensibility, as observed over the iliac crests and malleoli, and impairment of postural sensibility in the toes. One case has been reported in which the clinical findings indicated subacute com-

combined degeneration of the spinal cord and, if persistent paresthesias may be so interpreted, degeneration of the peripheral nerves (although the tendon reflexes were not impaired) These clinical findings disappeared after intensive intramuscular administration of liver extract

SUMMARY

Subacute combined degeneration of the spinal cord has come to involve a major problem that revolves around the type seen typically with pernicious anemia More than sixty associated conditions or causes have been advanced for combined degeneration that often is said to be "just like that of pernicious anemia" The legitimate and important question has been raised before as to the accuracy and implications of some of these observations and whether the typical clinical and pathologic picture does not carry with it an import that in some manner attaches specifically to a factor unknown but commonly associated with pernicious anemia

The funiculi of the spinal cord may be altered by many diseases and in many ways The differential diagnosis cannot always be made on clinical evidence alone Before a cause of subacute combined degeneration of the spinal cord like that which occurs in cases of pernicious anemia can rightly be assigned, typical and well developed clinical and pathologic observations must be brought forward as evidence On the basis of a survey of the important available literature, it appears that this familiar and challenging picture may be brought about by chronic alcoholism, gastric carcinoma, obstruction and fistulas of the intestinal tract, pernicious anemia, so-called prepernicious anemia and scurvy (this may have been a complication) It possibly may be similarly related to pancreatitis, pellagra and hemolytic icterus, and it has been in some manner associated with amyotrophic lateral sclerosis and a number of unclassified diseases

An important physiologic principle appears to be involved Careful hematologic studies, gastric analysis and an investigation of the presence of Castle's intrinsic factor, if facilities are available, possibly would lead to the disclosure of some one underlying cause, probably nutritional and in the nature of a deficiency

We have studied 77 cases in which there were signs of involvement of the posterior and of the lateral columns of the spinal cord and in which free hydrochloric acid was present in the gastric contents The latter finding practically eliminates pernicious anemia as a cause of the involvement When gradually developing, symmetrical, persistent paresthesias of the hands and feet are added, the clinical neurologic picture becomes that seen typically in cases of pernicious anemia There were 8 cases in which these symptoms were present, in 3 of these there

was no reason for believing that a nutritional factor entered into the cause, in the remaining 5 there was reason for thinking so, although we do not venture to say that the pathologic examination in these cases would have disclosed classic subacute combined degeneration of the spinal cord. To borrow a term from the serologic laboratory, occasional "false positive" results, which are indistinguishable clinically at a given time from the picture typically seen with pernicious anemia, may be observed. In cases in which the diagnosis is doubtful an examination of the spinal fluid increases the accuracy of the diagnosis. In none of these cases could the exact pathologic nature of the lesion in the cord be verified.

In a review of more than two hundred available articles on the subject of sprue it was found that only twenty included evidence of organic involvement of the nervous system.

Gastric analysis revealed the presence of free hydrochloric acid in 52 of the 93 cases of sprue and related conditions which have been observed at the clinic. The presence of free hydrochloric acid was regarded as presumptive evidence that no cases of pernicious anemia were included in this study. Neurologic examination was performed in 29 of the 52 cases.

In 11 of these 29 cases there was evidence of organic involvement of the nervous system. In 6 of these cases there had been continuous paresthesias of the hands and feet, in 6 cases the tendon reflexes were diminished or absent, and in 1 case they were increased, in 10 cases vibratory sensibility was impaired or absent, usually at both iliac crests and at the malleoli. Macrocytosis was present in 8 cases. One case has been reported in which the clinical findings indicated subacute combined degeneration of the spinal cord. These clinical findings disappeared after intensive intramuscular administration of liver extract.

ELECTROLYTE BALANCE DURING RECOVERY FROM MERCURY BICHLORIDE POISONING

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In the body fluids of patients suffering from acute mercury poisoning the changes in the concentration of electrolytes may be profound. Few other diseases are associated with a greater disturbance of acid-base equilibrium than is observed in this condition. Addison's disease,¹ diabetic coma² and heat cramps³ are examples of morbid conditions which are associated with recovery as the disordered equilibrium is corrected. Advanced renal insufficiency, on the other hand, is a disease with electrolyte imbalance which resists restoration to normal and ends with a disintegration of the chemical structure of the body.⁴ Acute mercury poisoning sometimes belongs in one category, sometimes in the other. In this communication there will be described the several changes in the concentration of electrolytes in a patient who recovered from acute and severe mercury poisoning.

The amount of mercury bichloride which was ingested was believed to have been 1 Gm. Usually this amount is not fatal,⁵ nevertheless, it

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4 Peters, J. P., Wakeman, A. M., Eisenman, A. J., and Lee, C. Total Acid-Base Equilibrium of Plasma in Health and Disease. X The Acidosis of Nephritis, *J. Clin. Investigation* **6** 517, 1929.

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was followed in this case by hematemesis, melena anuria, uremia and coma. Convalescence was satisfactory but was sufficiently slow to permit us to use and to evaluate several therapeutic procedures. Our principal interest in this communication is the presentation of data obtained during the correction of the disordered equilibrium. In addition there will be discussed other data which aid in the explanation of the secretion of urine by the various physiologic units in the kidney of vertebrates.

REPORT OF CASE

Mrs. L. N., a 32 year old housewife, was admitted to the Massachusetts General Hospital on March 16, 1935, having suffered from anuria for six days and from coma for thirty-six hours. Seven days before admission to the hospital she ingested about 1 Gm. of mercury bichloride during a temporary state of depression related to a postpuerperal psychosis. Shortly after the ingestion of the mercury salt, violent emesis began. The patient collapsed, and she was found unconscious on the bathroom floor by her relatives. The time between ingestion and emesis was estimated from five to fifteen minutes. After regaining consciousness the patient was taken to a local hospital and observed for seven days. During the first eighteen hours small amounts of dark, smoky urine were voided. Suppression followed, and during the ensuing six days less than 100 cc. of bloody urine was voided spontaneously or was obtained by catheter. During this time the patient vomited frequently each day, had unremitting bloody diarrhea and, in consequence, probably assimilated little or none of the food ingested. An infusion of 1,000 cc. of saline solution was given on March 12 and 14 and a transfusion of 500 cc. of whole blood on March 15.

The patient's past history was unimportant.

On admission to the Massachusetts General Hospital the patient was in a comatose state. The respiratory rate was rapid, and she perspired profusely and regurgitated small amounts of bile-colored fluid. There was dermatitis on the face. The pupils were contracted and did not react to light. The examination of the fundi revealed no abnormality. The auscultatory findings for the heart and lungs were normal. The heart rate at the apex was 100 per minute and regular. The blood pressure, which was 150 systolic and 100 diastolic when the patient entered the hospital, decreased after a few hours to 130 systolic and 80 diastolic and remained at this level during her stay in the hospital. Examination of the abdomen revealed slight epigastric tenderness. The rectal temperature was 37.8 C (100 F).

The results of the laboratory studies were as follows. The red blood cell count was 4,130,000. The white blood cell count was 17,800, with 80 per cent polymorphonuclears. The blood cells in the stained smear appeared to be normal. The hemoglobin value was 80 per cent (Tallqvist). The Hinton reaction of the blood was negative. The specific gravity of the urine was 1.008. There was a slight trace of albumin in the urine, as shown by the heat test. The urinary sediment contained many red and white blood cells. The tests for the presence of sugar and ketone bodies gave negative results. The first stools passed after the patient's admission to the hospital definitely showed the presence of blood.

A roentgenographic study of the esophagus, stomach and small intestines three weeks after the ingestion of the poison revealed no abnormality.

After the patient's admission to the hospital large amounts of sodium chloride were given parenterally, according to the method of Peters and his associates^{5a} During the first thirty hours a total of 100 cc of bloody urine was obtained by catheterization On March 18 the patient voided spontaneously 450 cc of cloudy urine During the remainder of her stay at the hospital the daily volume of urine was greater than 1,000 cc The volume of vomitus varied from 90 to 1,400 cc per day On March 21 80 milliequivalents of racemic sodium lactate was given intravenously A similar amount was given on two of the three following days From March 25 to 29 calcium lactate was given by mouth in amounts varying from 42 to 126 milliequivalents On March 29 a transfusion of 500 cc of whole blood was given

The mental condition of the patient improved during her stay in the hospital She was discharged on April 2 and returned to her home Two follow-up visits to the hospital were made The last visit took place five months after the ingestion of the mercury bichloride Except for a diminished concentration of hemoglobin, a slightly increased concentration of nonprotein nitrogen and a low urinary specific gravity, the results of studies at that time were normal

Methods—The determinations on the blood were made with specimens of arterial blood which were collected anaerobically Except for the specimens taken on March 16 and the second sample on March 21, all were obtained while the patient was fasting and at least eight hours after the last parenteral injection of the previous day Specimens of urine were collected in twenty-four hour amounts, preserved under toluene and stored at a temperature below 4 C The calculation of the p_H of arterial serum has been described⁶ On certain days observations were not made on equilibrated blood On these days the value for the carbon dioxide tension was derived from the data of Henderson,⁷ and the p_H was calculated The error in calculating p_H in this fashion is not significant The methods employed for analysis of blood and urine have been reported elsewhere⁸ This patient was not studied in the research ward, but she was under the constant supervision of graduate nurses, and the data regarding fluid and salt exchange are thought to be reliable

Blood—The data for the constituents of the plasma and whole blood are given in table 1 Severe acidosis was observed in the first specimen of blood, and as late as the morning of March 21, twelve days after the onset of the illness, the p_H had not exceeded 7.21 The acidosis was associated with a diminished alkali reserve, a diminished concentration of fixed base and an increased concentration of undetermined acid An unfavorable prognosis was given this patient

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TABLE 1—*Experimental Observations on Arterial Blood*

Date, 1915	Day of Illness	Whole Blood					True Plasma										Non protein Nitro gen, Mg per 100 Cc
		Total Carbon Dioxide, M Eq per Liter	Carbon Dioxide Tension, Mm of Hg	Oxygen Capacity, M Eq per Liter	Cell Volume, Cc per 100 Cc	<i>pH</i>	Total Fixed Base, M Eq per Liter	Sodium, M Eq per Liter	Cal cium, M Eq per Liter	Bicar bonate, M Eq per Liter	Chloride, M Eq per Liter	Phos phate, M Eq per Liter	Protei nate, M Eq per Liter	Urate, M Eq per Liter	Undeter mined Acid, M Eq per Liter	Sugar, Mg per 100 Cc	
March 16†	7	9.1	27.2*	6.92	34.9	7.19*	134.1	125.0	3.3	9.6	82.2	4.2	10.5	0.73	26.7	94	260
18	9	9.1	27.0	6.76	30.5	7.18	140.4	134.8		9.4	88.8		9.7	0.77		101	260
19	10		25.0*		32.6	7.20*	141.6	129.5	3.3	9.0	93.4	3.0	10.0	0.83	25.4	91	275
20	11	8.1	24.6	6.41	30.4	7.18	148.3	136.4		8.5	100.8		12.1	0.71		97	180
21	12	8.8	25.5*		29.8	7.21*	145.1	141.7	3.1	9.2	104.6	2.1	11.3			85	190
21†	12	11.2	26.7*		26.4	7.30*	143.4	134.3		12.0	105.7						
22	13	11.3	26.9*		27.6	7.29*	142.2	134.3		11.7	104.2		11.9	0.58			160
23	14	14.1	28.5	5.77	25.8	7.35	147.2	136.2	3.0	14.5	104.2	2.0	11.2	0.54	14.8		140
25	16	21.8	34.2	4.90	23.9	7.48	143.9	133.2		23.2	99.0		13.4				120
27	18	28.8	40.9	5.05	24.4	7.52	149.8	135.1	3.7	31.0	94.0	1.0	16.4	0.26	7.2		90
30	21	22.6	40.0	6.04	33.4	7.43	153.0	141.9	4.7	24.5	104.2	0.8	16.8	0.20	6.5		55
April 2	24	21.7	39.8	5.85	30.2	7.42	150.7	138.3		24.0	103.8		18.8	0.18			35
30	52	20.9	42.0	6.94	35.2	7.39	147.0	136.7		23.3	102.8		16.9	0.30			39
Aug 19	163			7.73	38.8		149.5	137.3	5.3	21.7	104.8	1.1	16.9				

* Calculated indirectly

† Blood drawn at 9 p. m.

because of the duration and severity of the acidosis. In a series of thirty-seven patients suffering from mercury poisoning, Peters and his associates^{5a} observed no recovery among those for whom the bicarbonate concentration was below 10 milliequivalents per liter. When this patient was admitted the bicarbonate concentration was 9.6 milliequivalents per liter, and it remained below 10 milliequivalents until March 21. The concentration of undetermined acid in the first specimen of blood was about 27 milliequivalents per liter. The acids which they replaced were principally bicarbonate and chloride. The exact nature of these undetermined acids is not known. Ketone bodies were not present in these specimens of urine, and it is assumed, therefore, that there was no ketonemia. The concentrations of lactate and sulfate were not determined.

The maximal depletion of plasma chloride was approximately 20 milliequivalents per liter, that of plasma sodium, approximately 15 milliequivalents per liter. These were observed in the first specimen of blood. The diminished concentration of these constituents was probably associated with a similar decrease in their concentration in the interstitial fluids.³ If this assumption is correct, the negative balance was great during the first week of illness. At least four processes were responsible for the depletion. 1. The diuresis which followed the ingestion of the mercury salt was probably accompanied with an increased excretion of sodium and chloride.⁹ 2. The excretion of gastro-intestinal juices during the excessive vomiting and diarrhea caused a further drain on the electrolytes of the body fluid.¹⁰ 3. The loss of electrolytes from sweating was probably great during the first days of illness. 4. There was an inadequate ingestion of the food and mineral salts which are normally consumed.

The treatment with saline solution parenterally during the first five days was accompanied with a return to normal of the concentrations of plasma sodium and chloride. On the morning of March 21 the sodium concentration was 141.7 milliequivalents per liter, and the chloride concentration was 104.6 per liter. In contrast to these changes was the consistently low concentration of bicarbonate. In spite of the administration of large amounts of base as sodium chloride, the alkali reserve did not increase until the evening of March 21. On this day 80 milliequivalents of racemic sodium lactate¹¹ was given intravenously. Twenty-four hours later the bicarbonate concentration had increased 2.8 milliequivalents per liter, and the p_H had increased from 7.21 to 7.30. The injections of racemic sodium lactate were continued until March 25. On this day the p_H was 7.48, and the bicarbonate concentration was 23.2 milliequivalents per liter.

9 MacNider, W. de B. On the Elimination of Phenolsulphonephthalein in Acute Mercuric Chloride Intoxication, *Proc Soc Exper Biol & Med* **18** 73, 1920. Fulton, M. N., Van Auken, H. A., Parsons, R. J., and Davenport, L. F. The Comparative Effect of Various Diuretics in Dogs, with Special Reference to the Excretion of Urine, Chloride, and Urea, *J Pharmacol & Exper Therap* **50** 223, 1934.

10 Gamble, J. L., and McIver, M. A. Body Fluid Changes Due to Continued Loss of the External Secretion of the Pancreas, *J Exper Med* **48** 859, 1928.

11 Hartmann, A. F., and Senn, M. J. Studies in the Metabolism of Sodium ι -Lactate. II. Response of Human Subjects with Acidosis to the Intravenous Injection of Sodium ι -Lactate, *J Clin Investigation* **11** 337, 1932. Hartmann, A. F. Treatment of Severe Diabetic Acidosis. A Comparison of Methods, with Particular Reference to the Use of Racemic Sodium Lactate, *Arch Int Med* **56** 413 (Sept) 1935.

From March 21 to 28 the increase in concentration of plasma bicarbonate was approximately 22 milliequivalents per liter. Simultaneous with this increase there was a decrease of 10 milliequivalents per liter in concentration of plasma chloride. The familiar reciprocal relationship between concentration of bicarbonate and concentration of chloride is shown in the chart that accompanies this article. During this period the concentration of total base increased 5 milliequivalents per liter, and the concentration of undetermined acid decreased about 19 milliequivalents per liter. Thus the sum of the increase of bicarbonate and base (27 milliequivalents) is approximately equal to the sum of the decrease of chloride and undetermined acid (29 milliequivalents).

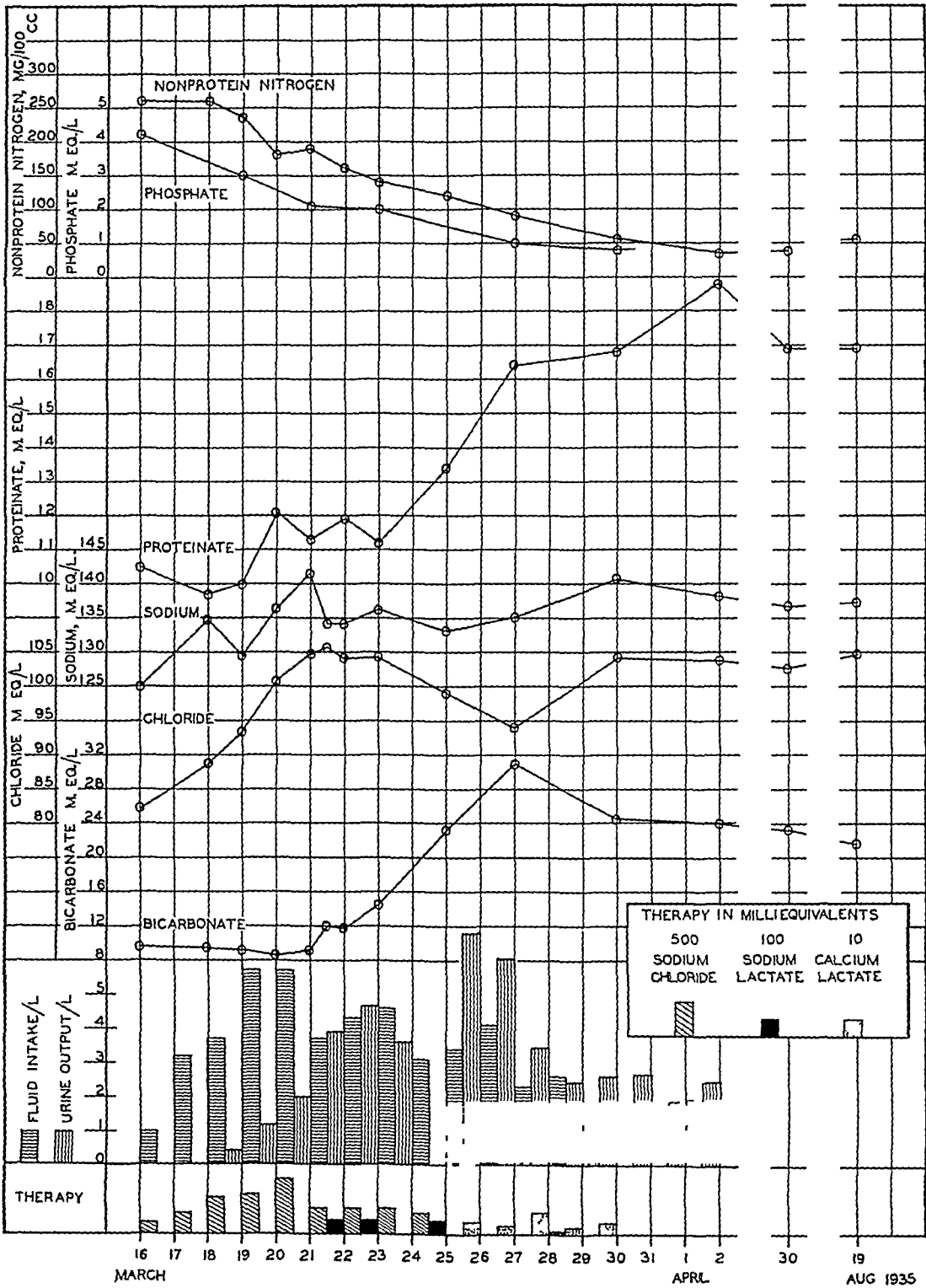
The decrease in concentration of total fixed base at the time of the patient's entry into the hospital was principally a depletion of the sodium fraction but not exclusively. The concentration of calcium in the first specimen of blood was 3.3 milliequivalents per liter. The concentration of ionized calcium in the same sample, calculated according to the method of McLean and Hastings,¹² was 1.9 milliequivalents per kilogram of water. This is below the average given by them for normal subjects. The ingestion of calcium lactate was begun on March 25. The return of the concentration of total calcium and ionized calcium toward normal was associated with the daily ingestion of this salt and a transfusion of whole blood on March 29. Four months after the patient's discharge from the hospital the concentration of serum calcium was 5.3 milliequivalents per liter.

The concentration of serum phosphate when the patient was admitted was 4.2 milliequivalents per liter, approximately five times normal. This increase was a function of at least two processes. 1. In certain disturbances of acid-base equilibrium an increased concentration of serum phosphate follows a diminution in concentration of serum calcium. 2. A characteristic sequela of renal insufficiency is an increase in the phosphate value.⁴ The concentration of this constituent decreased steadily during the patient's stay in the hospital, and on March 30 it was 0.8 milliequivalents per liter.

Associated with the increased concentration of serum phosphate was the increased concentration of nitrogenous products. On March 16 the concentration of nonprotein nitrogen was 260 mg per hundred cubic centimeters, and the urate value was 0.72 milliequivalents per liter. After the parenteral administration of large amounts of sodium chloride and water, the urinary flow was reestablished, and the concentration of nonprotein nitrogen decreased. The concentration of urate, however, remained at a high level for several days and began to decrease only after the concentrations of sodium and chloride in the plasma were normal. This may be interpreted as evidence that the kidney contributes to the metabolism of uric acid in the body, in addition to its function as the principal excretory organ for this substance.

The loss of protein and hemoglobin from the circulating blood probably was as large as 30 per cent. The concentration of plasma proteinate at the time of the patient's admission to the hospital was 10.5 milliequivalents per liter (4.9 Gm per hundred cubic centimeters expressed as plasma protein), and the oxygen capacity was 6.9 milliequivalents per liter. The concentration of plasma proteinate increased as the dietary intake of the patient approached normal. The concentration of hemoglobin in the blood, however, continued to decrease. On March 27

12 McLean, F. C., and Hastings, A. B. The State of Calcium in the Fluids of the Body. I. The Conditions Affecting the Ionization of Calcium, *J. Biol. Chem.* **108** 285, 1935.



Experimental data on the intake and output of fluid, the concentration of certain constituents of the blood and therapy. The urine excreted on March 24 was discarded.

the oxygen capacity was 18 milliequivalents per liter less than at the time of the patient's entry into the hospital, and five months after the onset of the illness it was still below the average value for women

The diminished concentration of proteinate and hemoglobin on entry can be accounted for by a loss of these substances from the circulating blood⁵¹ During the first three days of treatment there was a further decrease in the content of plasma proteinate After this transient decrease, which was produced by hydration, the proteinate concentration returned to normal The failure of the concentration of hemoglobin to return simultaneously is interesting The continued loss of blood did not appear to be sufficient to explain this discrepancy Damage to the hematopoietic system by the mercury bichloride seems to be a more acceptable explanation The patient was not weighed during the acute stages of her illness, and determinations of the blood volume were not made Quantitative data concerning dehydration must be deduced, therefore, from the protein and hemoglobin values This method is obviously unsatisfactory

The concentration of sugar in the plasma was normal in all determinations

Urine—The data for the intake of water and sodium chloride and for the urinary constituents are given in table 2 Electrolyte studies of the urine were not made until March 19 On this day nearly 6 liters of fluid was given, and the urinary volume was 1,190 cc The amount of base and chloride excreted as the urinary flow was established was surprising It was assumed that the tissues were suffering from salt depletion, and it was believed that they would retain most of the available salt This sequence was not observed On March 19 the concentration of chloride in the urine was 87 milliequivalents per liter, about 6 milliequivalents less than the concentration of plasma chloride Similar data were obtained for concentration of fixed base The failure of the body to keep back base and chloride may be attributed to the damage to the kidneys

The principal electrolyte in the total base of the urine was sodium This can be explained by the large amounts of sodium chloride which were given parenterally The absence of an increased excretion of potassium (calculated by difference) indicates that an excessive breakdown of tissue during anuria had not occurred This is consistent with the data for the excretion of total nitrogen and inorganic phosphate On March 19 and 20 less than 6 Gm of nitrogen was excreted daily The intake of protein on these days accounted for this amount of nitrogen

The comparison of the concentration of uric acid and inorganic phosphate in the urine with the concentration in the blood is of interest in relation to renal physiology On March 19 the concentration of urate in the urine was 0.68 milliequivalents per liter, and in the serum it was 0.96 milliequivalents per liter¹³ This gives a ratio of 0.7 if the calculation is based on water content On the same day the ratio of inorganic phosphate in the urine to that in the serum was 1 On March 23 the ratio for urate was 2.4 and for phosphate 1.5 The ratios continued to increase during recovery, and on March 30 the concentration of urate in the urine was approximately nine times greater than that in the serum, while the phosphate concentration in the urine was approximately five times greater than that in the serum

Six milligrams of phenolsulfonphthalein was injected intramuscularly on March 24 Approximately 2 per cent was excreted in the first hour after injection and the same amount in the second hour One week later a similar amount of

13 In this discussion of electrolyte ratios it is assumed that all the urate is present as acid and not bound by base

TABLE 2—Daily Observations on Intake and Ureay Output

[illegible]

dye was injected intravenously, and 20 per cent was excreted in the first fifteen minutes. At the end of two hours 48 per cent was excreted. In two subsequent tests, given on April 30 and August 19, 25 and 40 per cent, respectively, were excreted during the first fifteen minutes.

Albumin, blood cells and casts are observed frequently in the urine of patients suffering from mercury poisoning.¹⁴ The disappearance of these substances in this case required but a few days. The specific gravity of the urine did not exceed 1.010 during the patient's stay in the hospital or at the follow-up visits.

INDUCTIONS CONCERNING THE VERTEBRATE KIDNEY

The site of the damage to the renal architecture in acute experimental mercury poisoning is principally in the tubules.¹⁵ The glomeruli suffer less. The chemical findings which are presented in this communication are in agreement with these data. During the first days of treatment the respective concentrations of chloride, phosphate and urate in serum and urine were similar. At the time when the kidneys resumed the secretion of urine, the fluid passed was essentially a plasma filtrate, and the contribution to renal function by the tubules was minimal. This supposition is consistent with the data of Richards and his associates¹⁶ concerning the nature of the glomerular filtrate of the amphibian kidney. The urine was not exclusively a plasma filtrate, however, for dextrose was absent¹⁷ from the specimens obtained on March 17 and 18. This phenomenon may be accounted for in at least two ways. Either selective damage was done to the functioning area of the tubules or different segments of the tubules have different functions. The latter explanation

14 Frelberg, R. H., and Lashmet, F. H. A Quantitative Study of Renal Injury in a Case of Acute Poisoning by Bichlorid of Mercury, with a Note Regarding Treatment, *Am J M Sc* **189** 392, 1935.

15 Hayman, J. M., Jr., and Priestly, J. T. The Importance of Diuresis in the Treatment of Certain Cases of Mercuric Chlorid Poisoning, *Am J M Sc* **176** 510, 1928. Weiss, H. B. Mercuric Chlorid Poisoning, *Tr Sect Pharmacol & Therap, A M A*, 1923, p. 30. MacNider, W. de B. A Study of Acute Mercuric Chlorid Intoxication in the Dog, with Special Reference to the Kidney Injury, *J Exper Med* **27** 519, 1918.

16 Bordley, J., and Richards, A. N. Quantitative Studies of the Composition of Glomerular Urine. VIII The Concentration of Uric Acid in Glomerular Urine of Snakes and Frogs, Determined by an Ultramicroadaptation of Folin's Method, *J Biol Chem* **101** 193, 1933. Walker, A. M. Quantitative Studies of the Composition of Glomerular Urine. X The Concentration of Inorganic Phosphate in Glomerular Urine from Frogs and Necturi Determined by an Ultramicromodification of the Bell-Doisy Method, *ibid* **101** 239, 1933. Westfall, B. B., Findley, T., and Richards, A. N. Quantitative Studies of the Composition of Glomerular Urine. XII The Concentration of Chlorids in Glomerular Urine of Frogs and Necturi, *ibid* **107** 661, 1934.

17 Wearn, J. T., and Richards, A. N. Observations on the Composition of Glomerular Urine, with Particular Reference to the Problem of Reabsorption in the Renal Tubules, *Am J Physiol* **71** 209, 1924.

is consistent with the observations of Menten¹⁸ and Richards¹⁹ that only certain parts of the tubules are damaged by mercury poisoning. After the first days of relative tubular inactivity it is assumed that there was a rapid return of their function. This assumption is based on the increase in concentration of chloride, urate and phosphate in the urine. The data on the excretion of phenolsulfonphthalein dye further substantiates this hypothesis. Marshall²⁰ has shown that in uninjured kidneys this dye is excreted by the tubules. On March 24 only minimal amounts of the dye were excreted, while seven days later 48 per cent of the total amount injected was excreted.

SUMMARY

Studies of the blood and urine of a patient suffering from acute mercury poisoning are reported. After the ingestion of a sublethal dose of mercury bichloride there was a six day period of anuria. The observations reported began on the seventh day and continued through convalescence. Five months after the onset the patient had resumed her household duties, and in most instances the results of examination of the blood and urine appeared to be normal.

The changes in concentration of electrolytes and nonelectrolytes in the body fluids were (1) depletion of base and chloride, (2) an increased concentration of undetermined acid, (3) retention of phosphate and nitrogenous products and (4) loss of serum protein and hemoglobin. The treatment was devised to restore to normal the disordered acid-base equilibrium. The administration of large amounts of saline solution during anuria was thought to have been beneficial rather than injurious. The data presented are consistent with the interpretation that in acute mercury poisoning the principal renal damage is in the tubules.

18 Menten, M. L. Pathological Lesions Produced in the Kidney by Small Doses of Mercuric Chloride, *J. M. Research* **43** 315, 1922.

19 Richards, A. N. Direct Observations of Changes in Function of the Renal Tubules Caused by Certain Poisons, *Tr. A. Am. Physicians* **44** 64, 1929.

20 Marshall, E. K., Jr. The Secretion of Phenol Red by the Mammalian Kidney, *Am. J. Physiol.* **99** 77, 1931.

MECHANISM OF EXPERIMENTAL UREMIA

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In a previous communication¹ it was shown that changes in the electrolyte pattern of the cerebrospinal fluid of dogs produced by intracisternal injections caused muscular twitching, a rise in blood pressure and disturbances of breathing. The similarity of this syndrome to that exhibited by certain patients with renal insufficiency has led to a study of experimental uremia. In the present communication no attempt will be made to summarize the extensive literature on the subject. Discussions of previous work are to be found in the publications of Fishberg,² Becher³ and Harrison and Mason.⁴

EXPERIMENTAL METHODS

Dogs were used as experimental subjects. Measurements of the blood pressure were made by a modification of the technic of Ferris and Hynes,⁵ the cuff employed being similar to theirs but the passage of the pulse wave being determined by palpation of the dorsal artery of the hindfoot rather than by auscultation. The results obtained by this method were found to compare satisfactorily with the

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1 Resnik, H, Jr, Mason, M F, Terry, R T, Pilcher, C, and Harrison, T R. The Effect of Injecting Certain Electrolytes into the Cisterna Magna on the Blood Pressure, *Am J M Sc* **191** 835, 1936.

2 Fishberg, A M. Hypertension and Nephritis, ed 3, Philadelphia, Lea & Febiger, 1934.

3 Becher, E. Pathogenese, Symptomatologie und Therapie der Uramie, *Ergebn d ges Med* **18** 51, 1933.

4 Harrison, T R, and Mason, M F. Pathogenesis of the Uremic Syndrome *Medicine* **16** 1, 1937.

5 Ferris, H W, and Hynes, J F. Indirect Blood Pressure Readings in Dogs. Description of Method and Report of Results, *J Lab & Clin Med* **16** 597, 1931.

graphic records of mean blood pressure obtained by connecting a mercury manometer to the cannulated femoral artery of the opposite leg. The effect of epinephrine on the values obtained by the two methods is illustrated in chart 1.

After repeated measurements of the blood pressure for several days had been made as controls, uremia was produced by bilateral nephrectomy, bilateral ureteral ligation or ligation of the renal arteries. After the operation the animals were observed once or twice daily, the blood pressure being taken and symptoms recorded. Samples of blood and cerebrospinal fluid were obtained at various times both preoperatively and postoperatively for chemical analysis.

In addition to these observations on uremic animals, attempts were made to investigate the toxicity of some of the substances retained in the body of uremic dogs by injecting the compounds into normal animals.

The analytic determinations were made as follows: nonprotein nitrogen according to the method of Folin and Wu,⁶ plasma chloride according to Whitehorn's⁷ method, total serum calcium according to the Clark and Collip⁸ modification of the Kramer-Tisdall technic, inorganic phosphate according to Bodansky's⁹ modi-

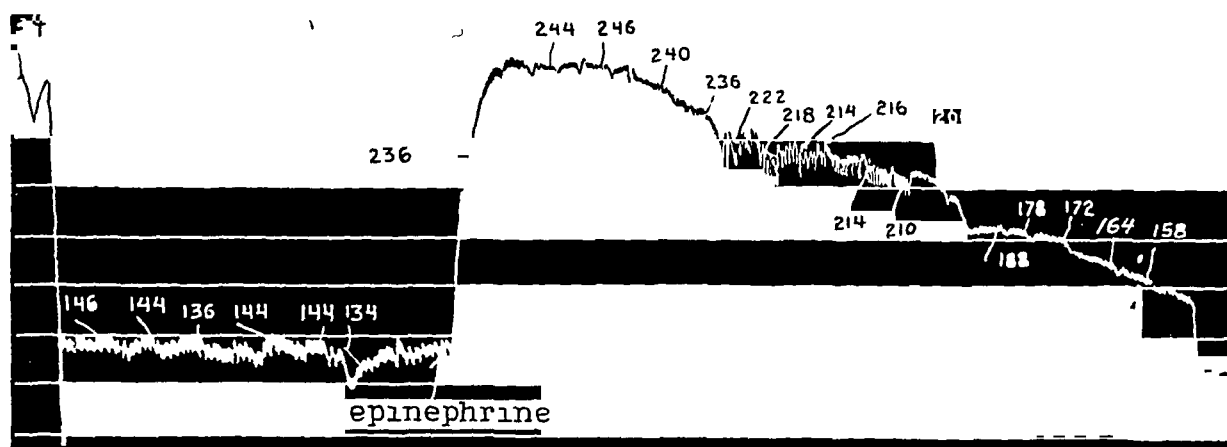


Chart 1—The curve passes from left to right. The distance between the adjacent horizontal lines indicates 20 mm of mercury. The femoral artery was cannulated on one side. Repeated measurements of blood pressure were made on the other leg by the cuff method mentioned in the text. The numbers on the record signify the readings obtained. As can be seen, the results of the two methods were in substantial agreement. Since the mercury manometer records the mean pressure rather than the actual systolic pressure, it is evident that the values obtained with the cuff method are somewhat below the systolic pressure and represent an approximation of the mean arterial pressure.

6 Folin, O., and Wu, H. A System of Blood Analysis, *J Biol Chem* **38** 81, 1919.

7 Whitehorn, J. C. A Simplified Method for the Determination of Chlorides in Blood or Plasma, *J Biol Chem* **45** 449, 1921.

8 Clark, E. P., and Collip, J. B. A Study of the Tisdall Method for the Determination of Blood Serum Calcium with a Suggested Modification, *J Biol Chem* **63** 461, 1925.

9 Bodansky, A. Determination of Inorganic Phosphate, Beer's Law and Interfering Substances in the Kuttner-Lichtenstein Method, *J Biol Chem* **99**, 197, 1932.

fication of the Kuttner-Cohen¹⁰ method, carbon dioxide content with the Van Slyke-Neill¹¹ manometric apparatus, p_{H} of plasma and cerebrospinal fluid by the Hastings-Sendroy¹² bicolorimetric procedure, ionized calcium of serum and cerebrospinal fluid by the frog-heart method of McLean and Hastings,¹³ blood phenols by the Rakestraw¹⁴ adaptation of the method of Folin and Denis¹⁵ and guanidine according to the directions of Minot and Dodd¹⁶. It should be noted that the latter two methods are not highly specific. By the former method certain related compounds as well as phenols are measured, likewise, by the latter method substances probably related to guanidine are measured along with guanidine itself.

A THE CLINICAL PICTURE OF EXPERIMENTAL ANURIA IN DOGS

The clinical symptoms were similar to those described by Herter¹⁷ and are summarized in table 1. During the first twenty-four hours the animals usually appeared to be normal except for slight weakness, which could be ascribed to the operative procedure. Gastro-intestinal disturbances, characterized by vomiting and occasionally by diarrhea, usually appeared about forty-eight hours after the operation. Changes in blood pressure were observed in most of the animals. After ureteral ligation the blood pressure tended to be elevated. Inconstant changes were observed after bilateral nephrectomy, some of the animals displaying a definite elevation on the second and third postoperative days, followed by hypotension in almost all the animals on the fourth day. The reasons for differences in behavior of the animals as regards blood pressure will be discussed later.

The most striking changes had to do with the nervous system. On the second and third postoperative days many of the animals exhibited an increase in muscular irritability which subsequently disappeared.

10 Kuttner, T, and Cohen, H. R. The Micro-Estimation of Phosphorus and Calcium in Pus, Plasma and Spinal Fluid, *J Biol Chem* **75** 517, 1927.

11 Van Slyke, D. D., and Neill, J. M. The Determination of Gases in Blood and Other Solutions by Vacuum Extraction and Manometric Measurement, *J Biol Chem* **61** 523, 1924.

12 Hastings, A. B., and Sendroy, J., Jr. The Colorimetric Determination of Blood p_{H} at Body Temperature Without Buffer Standards, *J Biol Chem* **61** 695, 1924.

13 McLean, F. C., and Hastings, A. B. Biological Method for Estimation of Calcium Ion Concentration, *J Biol Chem* **107** 337, 1934.

14 Rakestraw, N. W. A Quantitative Method for the Determination of Phenols in Blood, *J Biol Chem* **56** 109, 1923.

15 Folin, O., and Denis, W. A Colorimetric Method for the Determination of Phenols (and Phenol Derivatives) in Urine, *J Biol Chem* **22** 305, 1915.

16 Minot, A. S., and Dodd, K. Guanidine Intoxication. A Complicating Factor in Certain Clinical Conditions of Children, *Am J Dis Child* **46** 522 (Sept.) 1933.

17 Herter, C. A. The Results of Experimental Nephrectomy in Dogs as Bearing upon the Uraemic State, *M Rec* **52** 280, 1897.

Apathy and weakness beginning on the second day were progressive, and stupor frequently occurred by the fourth day, however, true coma was rarely observed. Convulsions were occasionally encountered in these later stages.

The anuric animals, of course, displayed a steady rise in the non-protein nitrogen content of the blood. There was a less marked diminution in the chloride content of the plasma (chart 2).

Two distinct impressions were gained by the observation of anuric dogs. First, the general condition was similar to that of patients with renal insufficiency, and second, each animal behaved as if its nervous system were being subjected to two antagonistic influences, one tending to stimulate it and the other to depress it. In some animals the former

TABLE 1—Symptoms Observed in Dogs with Experimental Anuria

Operative Procedure	Days After Operation	Number of Animals Observed	Disturbances of Nervous System								Respiratory Disturbances
			Average Changes in Blood Pressure, Mm Hg	Manifestations of Depression		Manifestations of Stimulation			Gastro Intestinal Disturbances		
				Weakness or Apathy	Stupor or Coma	Twitching	Convulsions	Excitement	Vomiting	Diarrhea	
Bilateral nephrectomy	1	8	— 4	+	0	+	0	0	0	0	+
	2	7	— 2	+++	0	++	0	+	+	0	+
	3	8	+ 1	+++	0	++	0	+	+++	0	0
	4	7	—28	++++	++	+++	++	0	+++	++	0
Ligation of both ureters	1	14	+ 2	++	+	0	0	0	+	0	0
	2	11	+16	++	0	+	0	+	+++	0	—
	3	13	+33	+++	+	++	+	0	++	0	+
	4	5	+19	++++	0	++	0	0	++	+	0

* + indicates observed in 25 per cent or less of the animals, ++, observed in 26 to 50 per cent of the animals, +++, observed in 51 to 75 per cent of the animals, and +++++, observed in more than 75 per cent of the animals.

influence had the ascendancy, in some the latter was more outspoken. More frequently an animal would successively display symptoms of stimulation and then of depression, and not uncommonly, although paradoxically, the same animal at a given time would exhibit signs of both depression and stimulation of the nervous system. An adequate explanation of the nature of these influences seemed to be essential in understanding the mechanism of experimental uremia.

B THE RELATIONSHIP OF RETENTION OF INORGANIC PHOSPHATE AND CALCIUM ION DEFICIENCY TO UREMIA

A number of observations support the view that diminution in the calcium ion concentration of body fluids is responsible for the increased neuromuscular irritability exhibited in uremia and that this diminution is related to retention of inorganic phosphate. 1. Renal insufficiency is associated with an increase in the inorganic phosphate content of the

serum (de Wesselow¹⁸) 2 The decline in calcium content of the serum of patients with uremia is greater than that to be expected as a result of coexistent deficiency of plasma protein (Peters and Van Slyke¹⁹) and is associated with a fall in the ionized fraction (McLean and Leiter²⁰) 3 Intravenous injection of solution of alkaline or neutral sodium phosphate produces muscular twitching (Binger²¹) 4 More recent investigations (Hastings²² and Resnik, Mason, Teriy, Pilcher and Harrison¹) have indicated that diminution in the calcium ions of the tissues of the central nervous system, as evidenced by a deficit in the cerebrospinal fluid, produced by the intracisternal injection of solution of inorganic phosphate, oxalate or citrate, causes muscular twitch-

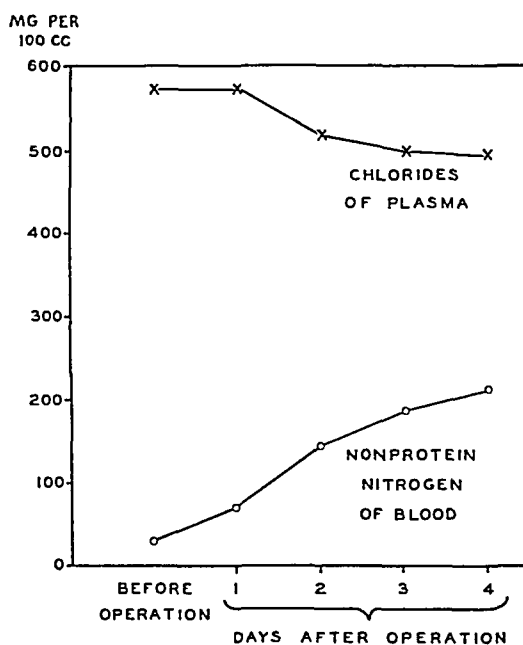


Chart 2—The average change in six dogs with experimental anuria. The curves illustrate the steady increase in nonprotein nitrogen and the slight diminution in plasma chloride following the onset of anuria.

ing, stertorous breathing and an increase in blood pressure—a syndrome resembling that seen in certain patients with uremia. Similar doses administered intravenously were entirely ineffective, although larger doses produced the same effects after a latent period of from fifteen

18 de Wesselow, O. L. V. On the Phosphorus and Calcium of the Blood in Renal Disease, *Quart J Med* **16** 341, 1923

19 Peters, J. P., and Van Slyke, D. D. Quantitative Clinical Chemistry Interpretations, Baltimore, Williams & Wilkins Company, 1935

20 McLean, F. C., and Leiter, L. The State of Calcium in the Blood in Nephritis and Uremia, *J Clin Investigation* **14** 705, 1935

21 Binger, C. Toxicity of Phosphates, in Relation to Blood Calcium and Tetany, *J Pharmacol & Exper Therap* **10** 105, 1917

22 Hastings, A. B. Personal communication to the authors

minutes to an hour, as was true in the experiments of Binger²¹ The protocols of Storti's²³ experiments on the effects of intravenous injections of oxalate also indicated a lag in the development of tetany

These observations suggested that the muscular twitching of uremia produced by calcium ion deficiency may be of central rather than peripheral origin In order to investigate this the relationships between the symptoms and the alterations in the ionized calcium and inorganic phosphate concentrations of serum and cerebrospinal fluid were investigated in a series of anesthetized dogs²⁴ after the administration of large intravenous injections of a mixture of primary and secondary sodium phosphate (p_H , 7.4) A typical result is shown in chart 3, which indicates that the onset of twitching was related to decline of the ionized calcium and increase in inorganic phosphate of the cerebrospinal fluid rather than to changes taking place in the serum²⁵

Aside from the muscular twitching the animals receiving intravenous injections of sodium phosphate displayed shivering, tremor, rigidity of the extensor muscles and occasional convulsions Respiration was usually rapid and frequently stertorous, and in some instances it was of a typically Cheyne-Stokes character In some of the dogs an exaggerated forcefulness of the heart beat shook the chest This phenomenon has been observed also in uremic dogs in consequence of experimental anuria

Observations on a series of nephrectomized dogs indicated that in this condition the onset of twitching is more nearly related to the increase of inorganic phosphate in the cerebrospinal fluid than to the increase in the serum When sodium phosphate was administered to these nephrectomized dogs, the onset of twitching was hastened, however, the onset still paralleled the rise in the inorganic phosphate, content of the cerebrospinal fluid, rather than that of the serum Illustrative data for four dogs are given in chart 4

Studies of the inorganic phosphate, total and ionized calcium contents of serum and cerebrospinal fluid of a series of normal dogs, of dogs in which experimental anuria had been produced shortly before and of dogs which had been anuric three or four days again indicated that the changes in the serum preceded those in the cerebrospinal fluid

23 Storti, E Ueber die Frage der Hypocalcämie bei Niereninsuffizienz Beziehungen zwischen Hypocalcämie und Oxalsaureretention, *Ztschr f d ges exper Med* **97** 35, 1935

24 Symptoms in response to the injections of sodium phosphate varied according to the anesthetic employed The symptoms were most pronounced in unanesthetized animals, least marked in those receiving pentobarbital sodium and intermediate when morphine was used

25 The intracisternal administration of calcium salts immediately abolished or markedly diminished muscular twitching in dogs with either experimental phosphate intoxication or experimental anuria The effect would last for several hours

and that the symptoms of severe renal insufficiency were attended by a decrease in the ionized calcium and an increase in the inorganic phosphate of the cerebrospinal fluid, although some exceptions were noted (table 2)

Comparisons were made also between the inorganic phosphate and ionized calcium contents of the cerebrospinal fluid of patients with renal insufficiency (some of whom had symptoms of uremia) and those of patients without renal disease. These data (table 3) indicate that there tends to be an elevation of inorganic phosphate and a diminution

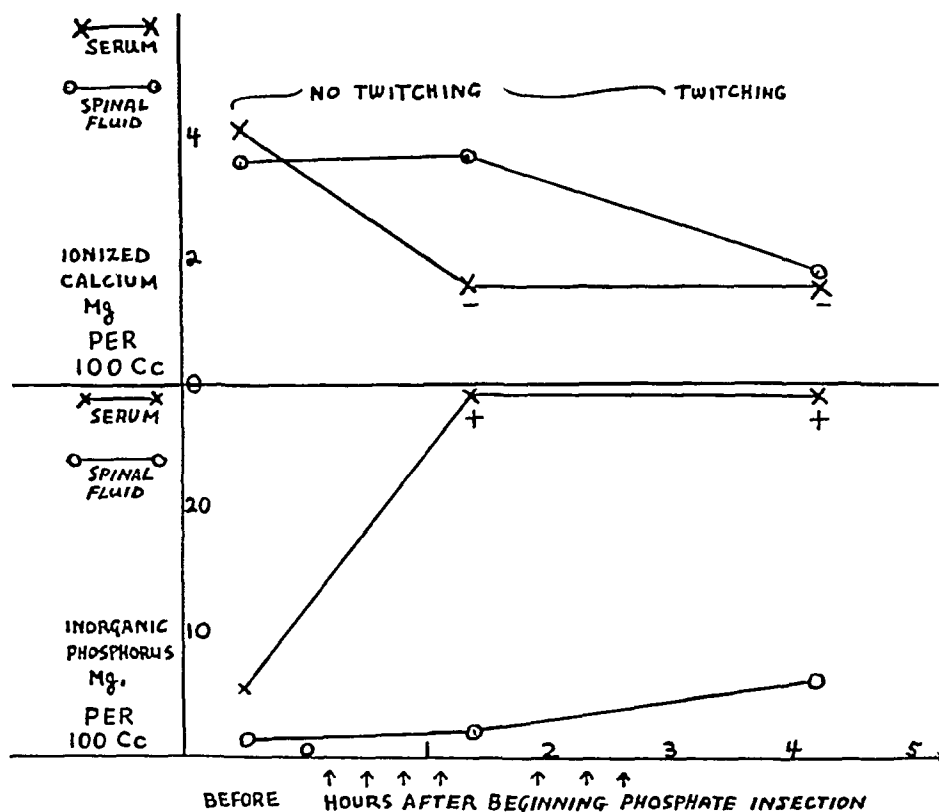


Chart 3—After the repeated intravenous administration of sodium phosphate (each injection containing 50 mg of phosphorus per kilogram of body weight), a rapid increase in the phosphate and a decrease in the ionized calcium of the blood were noted, with little or no immediate change in the composition of the cerebrospinal fluid. However, the frequent twitching did not begin until after several hours, at which time the corresponding alterations had begun to be apparent in the cerebrospinal fluid. The onset of twitching appeared to be related to alterations in the cerebrospinal fluid rather than to changes in the blood. Each arrow indicates the intravenous injection of 50 mg of phosphorus.

of ionized calcium in the cerebrospinal fluid of patients with renal insufficiency.²⁶

26 Five patients with renal insufficiency who exhibited increased neuromuscular irritability were given calcium salts intracisternally. In four the twitching was temporarily abolished or markedly diminished by this therapy.

The foregoing data indicate that the occurrence of muscular twitching in experimental uremia is related to a decrease in the calcium ion concentration of the cerebrospinal fluid ²⁷ brought about by the retention of metabolites. It is doubtful if this reduction is to be ascribed entirely to the accumulation of inorganic phosphate, although it tends to parallel this accumulation ²⁸. It seems likely that the accumulation of oxalate (Becher ³), citrate or some as yet unknown substances behaving like

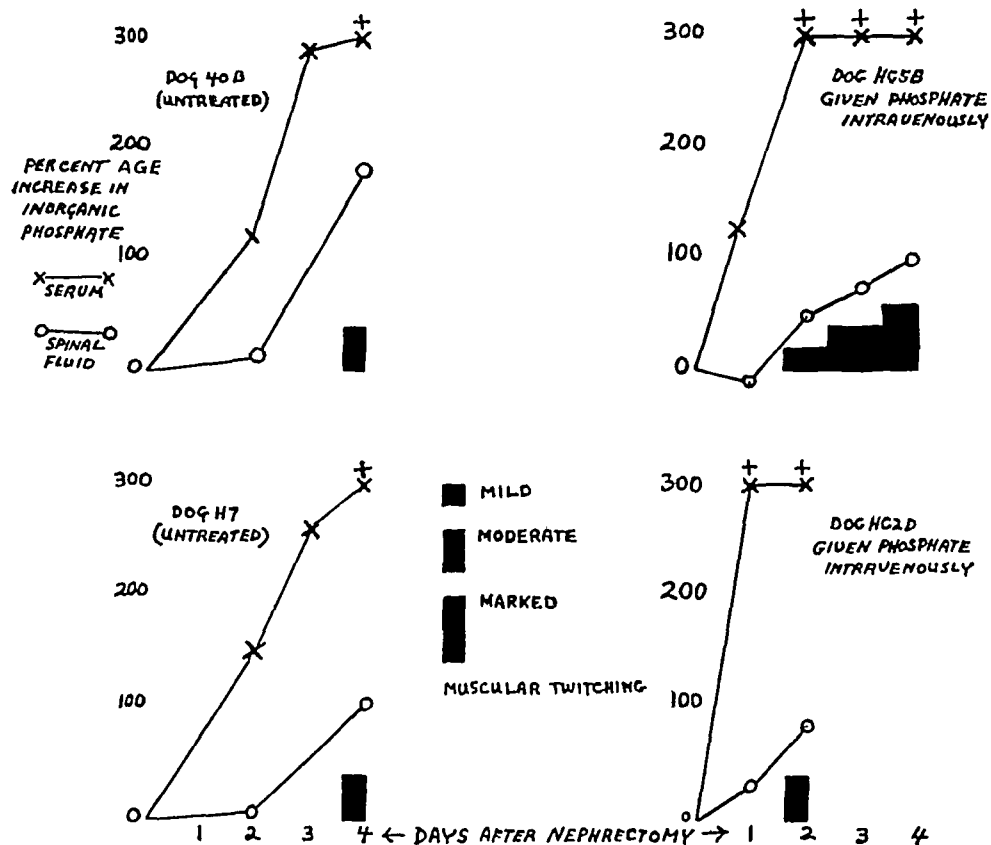


Chart 4—The two dogs, observations for which are depicted on the right, received daily injections of sodium phosphate (at p_H 7.4). Twitching developed the second day after nephrectomy, while the untreated animals, values for which are depicted on the left, did not display twitching until the fourth day of anuria. In all the animals the onset of twitching appeared to be related to increased concentration of phosphate in the cerebrospinal fluid rather than in the serum.

²⁷ This statement applies only to the increased neuromuscular irritability of the symptom complex of uremia. It does not imply that the tetany associated with calcium deficiency (such as spasmophilia) is of central rather than peripheral origin. We have not studied these conditions.

²⁸ Moderate variations in the concentrations of inorganic phosphate of the standard solutions used in the frog heart assay make no immediate appreciable difference in the calcium ion concentration of these solutions.

citrate plays an augmentative or predominant rôle in suppressing the ionization of calcium²⁹

If it is granted that the composition of the cerebrospinal fluid reflects the composition of the fluid intimately bathing the cells of the central nervous system a fall in calcium ion concentration of the cere-

TABLE 2—*Phosphorus and Calcium in Serum and Spinal Fluid of Dogs in Relation to Renal Insufficiency*

Group	Arterial Serum			Cerebrospinal Fluid		
	Inorganic Phosphorus, Mg per 100 Cc	Total Calcium, Mg per 100 Cc	Ionized Calcium, Mg per 100 Cc	Inorganic Phosphorus, Mg per 100 Cc	Total Calcium, Mg per 100 Cc	Ionized Calcium, Mg per 100 Cc
Normal dogs						
Number of observations	9	5	8	9	10	9
Highest	5.5	11.3	5.0	1.6	5.5	5.1
Lowest	2.9	10.5	3.3	1.1	4.7	3.8
Average	4.0	10.9	4.4	1.3	5.3	4.3
Dogs with early renal insufficiency						
Number of observations	5	3	7	11	5	8
Highest	12.5	12.1	5.0	1.8	6.1	5.0
Lowest	5.9	11.1	1.6	1.2	4.2	3.1
Average	9.6	11.7	3.0	1.5	5.5	4.1
Dogs with renal insufficiency						
Number of observations	6	3	2*	5	4	6
Highest	26.6	12.1	2.8	3.8	6.8	4.9
Lowest	16.6	5.7	2.5	1.7	5.1	0.8
Average	21.7	9.9	2.7	2.5	6.2	3.0

* In most of the animals with severe renal insufficiency the serum had toxic effects on the frog heart, and the amount of ionized calcium could not be satisfactorily measured

TABLE 3—*Inorganic Phosphorus, Total Calcium and Ionized Calcium in Cerebrospinal Fluid of Patients With and Without Renal Insufficiency*

Group	Inorganic Phosphorus, Mg per 100 Cc				Total Calcium, Mg per 100 Cc				Ionized Calcium, Mg per 100 Cc			
	Number of Observations	Highest	Lowest	Average	Number of Observations	Highest	Lowest	Average	Number of Observations	Highest	Lowest	Average
Control patients (with out renal insufficiency)	20	1.7	0.7	1.3	53	5.5	4.2	4.9	39	5.6	3.5	4.3
Patients with renal in sufficiency	16	4.5	0.8	2.7	17	5.6	3.5	4.7	8	4.3	3.3	3.8

29 Tweedy, W. R., and McNamara, E. W. Effect of Administration of Parathyroid Extract on Serum Calcium Level in the Nephrectomized Rat, *Proc Soc Exper Biol & Med* 35:414, 1936. These authors have reported that in nephrectomized rats treated with parathyroid extract hypercalcemia does not develop. They have stated the opinion that mobilization of calcium stores is deficient in this condition. This may be another mechanism tending to produce calcium deficiency in the uremic state.

brospinal fluid is indicative of a "central" deficiency of calcium ions. Increase in the inorganic phosphate content of the cerebrospinal fluid appears in many instances to be coincident with the establishment of this deficit.

Exceptions to the relationships just described were frequently encountered. 1. Occasionally dogs exhibited twitching without serious alterations in the levels of ionized calcium and inorganic phosphate in the cerebrospinal fluid.³⁰ 2. Frequently in the final "depressed" phase of uremia, twitching was absent in spite of considerable diminution in the ionized calcium and large increases in the inorganic phosphate concentration of the cerebrospinal fluid. Indeed, increased neuromuscular irritability frequently preceded the depressed phase at a time when the chemical alterations were much less marked.

Accordingly, it became necessary to search for factors which might call forth motor irritability without depleting the calcium ion concentration and which might inhibit their appearance in spite of an existing "central" deficit of calcium ions.

C THE RELATIONSHIP OF PHENOL AND RELATED SUBSTANCES TO UREMIA

The inhibiting effects of anesthesia on the twitchings manifested in experimental intoxication due to sodium phosphate suggested that the retention of substances having a narcotic action might account for the absence of neuromuscular irritability in spite of a "central" deficit of calcium ions. The extensive researches of Becher³¹ have furnished strong evidence that the constant occurrence of apathy and weakness in the earlier phases of uremia and the frequent development of stupor and coma in the later phases are consequences of the retention of free phenols. We have therefore undertaken experiments to elucidate further the relationship of these compounds to the symptom complex of uremia.

Experimental Phenol Intoxication—After the intravenous injection of nonlethal doses of phenol and paracresol into dogs a characteristic syndrome develops. Swimming movements are immediately displayed. These are followed by tremor and salivation, lasting several minutes. As these manifestations subside, weakness and apathy, with marked ataxia, are noted.

30 Salvesen, H. A. Die Beziehungen zwischen den uramischen Muskelzuckungen und den pathologisch-chemischen Blutbefunden, *Ztschr. f. klin. Med.* **115** 522, 1931. Peters, J. P. Salt and Water Metabolism in Nephritis, *Medicine* **11** 435, 1932. These authors have shown that muscular twitching may occur in patients with uremia in the absence of outspoken elevation of the inorganic phosphate content of the serum.

31 Becher, E. Studien über die Pathogenese der echten Uramie, *Zentralbl. f. inn. Med.* **46** 369 (April 25) 1925.

A somewhat similar syndrome is produced by the intraperitoneal injection of phenol and paracresol into mice. Tremor appears in a few minutes, along with weakness and stupor, the latter lasting for an hour or longer after the tremor has disappeared. When minimal lethal doses are administered, death may not occur for twelve hours or more. During this time the mouse lies on its side, unable to move and barely responsive to stimuli, apparently in a comatose state. Section of the kidneys of these mice have shown well marked renal damage, especially tubular degeneration.

These findings support the views of Becher, who has claimed that phenol retention as a result of renal disease tends to aggravate further the underlying disorder of the kidneys. According to Becher, chronic phenol poisoning in man produces a syndrome characterized by fatigue, emaciation, sleeplessness, weakness, hypothermia and finally stupor. He has emphasized the fact that the free phenol content of the blood of certain nephritic patients may be as high as that of patients with chronic phenol intoxication.

The Effect of Phenol on the Response to Intracisternally Injected Inorganic Phosphate—The syndrome produced by the intracisternal injection of substances tending to reduce the calcium ion concentration of the fluid bathing the central nervous system, such as phosphate, oxalate and citrate, has been described by Resnik, Mason, Terry, Pilcher and Harrison¹. Similar injections of sodium phosphate were made after the administration of paracresol either intracisternally or intravenously. The usual manifestations of twitching respiratory stimulation and increase in blood pressure were completely inhibited. Typical results are illustrated in chart 5.

The Phenol Content of Blood and Cerebrospinal Fluid of Dogs With Experimental Anuria—The results of observations made on normal dogs and dogs with experimental anuria of from two to four days' duration are given in table 4. Data on the phenol content of the blood of patients are found in table 5. It is evident that the concentration of phenol in body fluids is increased in states of renal insufficiency. The procedure we have employed for determining the phenol content¹⁴ is not highly specific and probably determines a number of other substances, such as diphenols, dioxybenzenes, oxyacids and related compounds, as well as free phenols, however, Becher²¹ has obtained similar results using an apparently more specific method.

Because the phenol content of body fluids is increased in uremia and because it has been shown that experimental phenol intoxication in animals and chronic phenol intoxication in man² are characterized by symptoms of depression and narcosis closely simulating certain symptoms of the uremic complex, it seems likely that instances of uremia lacking

in increased neuromuscular irritability in spite of "central" deficit of calcium ions are to be explained on the basis of the antagonistic action of retained phenols. This concept is materially strengthened by the experimental demonstration of the antagonistic action which has been described.

D THE RELATION OF GUANIDINE³² TO UREMIA

The manifestations of increased motor irritability in uremia are occasionally encountered both clinically and experimentally in the absence of evidence of an existing deficiency of calcium ions, e g, when the inorganic phosphate content of the serum is only slightly elevated.

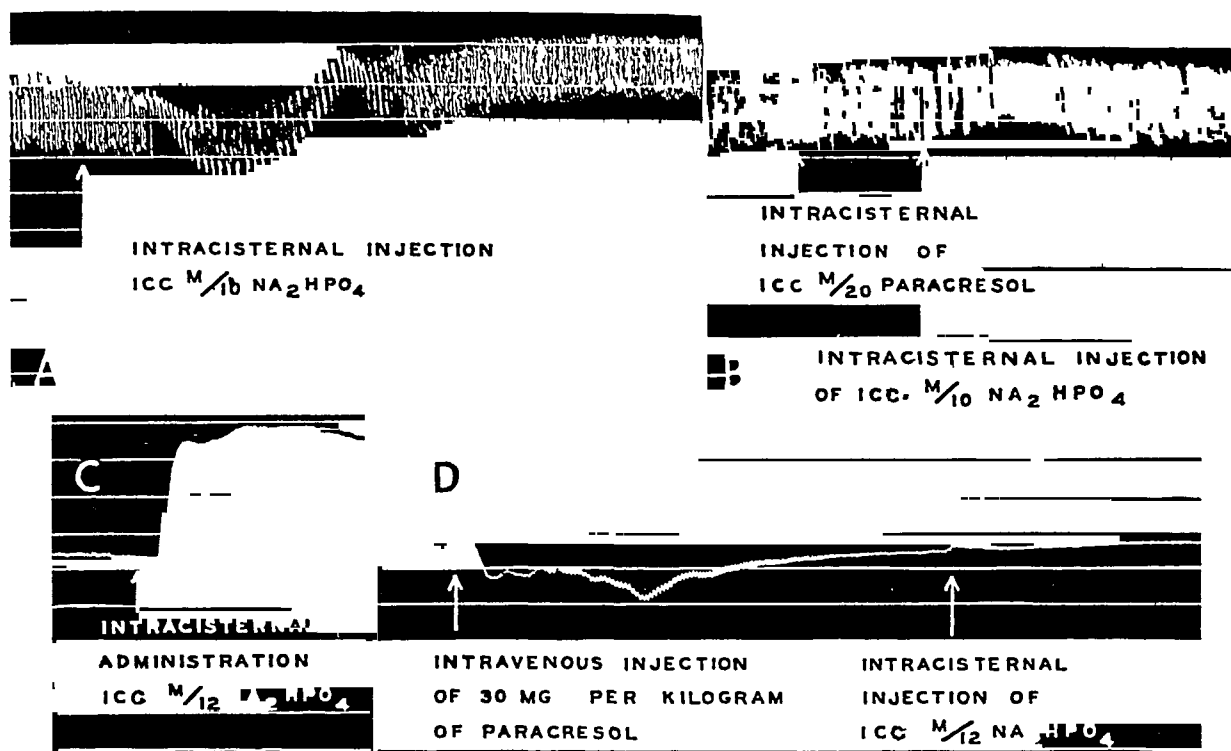


Chart 5—The curves pass from left to right. The distance between adjacent horizontal lines designates 20 mm of mercury. *A*, the intracisternal administration of disodium hydrogen phosphate caused an increase of approximately 30 mm of mercury. *B*, after the blood pressure had returned to the control level, paracresol was injected intracisternally and followed by disodium hydrogen phosphate. Only the slightest increase in blood pressure occurred. *C*, in another dog a rise of 70 mm in blood pressure was produced by phosphate. *D*, the same compound, when injected after the intravenous administration of paracresol, had practically no effect.

³² Study of the significance of guanidine in health and in disease has been hampered by lack of specific methods for the determination of this substance in body fluids. In this paper "guanidine" will designate the substance or substances giving the Sakaguchi, or nitroprusside, reactions, and guanidine will be reserved for the organic base itself.

and that of the cerebrospinal fluid is within normal limits. In these instances the twitchings must be initiated by a different mechanism, and there is some evidence that guanidine and/or its derivatives are important factors in the production of these and certain other signs of the uremic complex. 1 Foster³³ isolated from the serum of certain patients with uremia a toxic organic base which caused twitching, rapid breathing, convulsions and death when injected into guinea-pigs. The chemical properties of this substance suggest that it was guanidine or a guanidine derivative. 2 Several observers (Pffner and Meyers,³⁴ de Wesselow and Griffiths,³⁵ Bohn and Schlapp³⁶ and Kleeberg and Schlapp³⁷) have observed increases in the "guanidine" content of the

TABLE 4—*Free Phenols* of the Blood and Cerebrospinal Fluid of Normal Dogs and Dogs with Renal Insufficiency*

Material Analyzed	Normal Dogs		Dogs with Experimental Anuria	
	Number of Observations	Free Phenols, Mg % (Average Value)	Number of Observations	Free Phenols, Mg % (Average Value)
Blood	6	3.7	16	8.0
Cerebrospinal fluid	5	2.0	9	6.6

* The method used measures not only phenols but certain related compounds

TABLE 5—*Guanidine and Phenols in the Blood of Patients With and Without Renal Insufficiency*

Group	Guanidine, Mg per 100 Cc				Free Phenols, Mg per 100 Cc			
	No of Observations	Highest	Lowest	Average	No of Observations	Highest	Lowest	Average
Control patients (without renal insufficiency)	12	0.48	0.32	0.40	10	4.6	2.3	3.1
Patients with renal insufficiency	9	6.48	0.44	2.09	12	9.6	2.5	6.3

33 Foster, N. B. The Isolation of a Toxic Substance from the Blood of Uremic Patients, *Tr. A. Am. Physicians* **30** 20, 1915

34 Pffner, J. J., and Meyers, V. C. Colorimetric Estimation of Methylguanidine in Biological Fluids, *Proc. Soc. Exper. Biol. & Med.* **23** 830, 1926, On Colorimetric Estimation of Guanidine Bases in Blood, *J. Biol. Chem.* **87** 345, 1930

35 de Wesselow, O. L. V., and Griffiths, W. J. Blood Guanidine in Hypertension, *Brit. J. Exper. Path.* **13** 428, 1932

36 Bohn, H., and Schlapp, W. Untersuchungen zum Mechanismus des blassen Hochdrucks. Der Guanidingehalt des Blutes beim blassen und roten Hochdruck, *Zentralbl. f. inn. Med.* **53** 571, 1932

37 Kleeberg, J., and Schlapp, W. Ueber die Auffindung von uramieerzeugenden Stoffen, *Ztschr. f. physiol. Chem.* **188** 81, 1930

blood of some (but not all) patients with renal insufficiency. Administration of guanidine produces under certain conditions a symptom complex closely resembling that of uremia. For these reasons certain experiments were performed in order to elucidate further the rôle of guanidine in the uremic state.

Experimental Guanidine Intoxication—The clinical picture produced by the experimental administration of guanidine in a large series of dogs was found to depend on dosage, site of injection and kind of anesthetic employed. In unanesthetized dogs small doses given intravenously usually cause a fall in blood pressure, while intracisternal administration causes a rise in blood pressure. The duration of the pressor effect is brief. Toxic doses administered subcutaneously are followed after about an hour by salivation, apathy, vomiting, itching and diarrhea. Incoordination, ataxia and fibrillary tremors followed by clonic twitching and convulsions are commonly observed. When larger doses are given, the phase of nervous hyperirritability may pass rapidly into one of profound depression, in which the animal lies in a semicomatose state from which he can be aroused only with difficulty. For the first hour after the injection the blood pressure remains unchanged or falls slightly. During the second hour a definite rise occurs (30 to 40 mm of mercury) and is maintained for three or four hours, followed by a fall to normal or subnormal levels as the intoxication becomes more profound. If the dose used produces a fatal termination, this drop in blood pressure is progressive, the animal dying after a period of circulatory collapse of variable length. At autopsy evidence of marked peripheral capillary damage is encountered. Patchy hemorrhagic gastroenteritis is a constant finding. The circulatory features of guanidine have been studied by Minot.³⁸

We have confirmed the observation of Major and Weber³⁹ that after the intravenous injection of a large dose of guanidine or methyl guanidine into an anesthetized dog, there is a prompt elevation in blood pressure which may be sustained for an hour or longer. Doses too small to be effective intravenously were found to be markedly pressor when injected into the cisterna magna, indicating that guanidine has a "central" action, in addition to the peripheral pressor effect which was demonstrated by Goldblatt and Karsner.⁴⁰

The "Guanidine" Content of the Blood and Cerebrospinal Fluid of Dogs with Experimental Uremia—The data obtained for uremic dogs

38 Minot, A. S., and Keller, M. Circulatory Failure Associated with Guanidine Intoxication, *J Pharmacol & Exper Therap* **60** 32, 1937.

39 Major, R. H., and Weber, C. J. Possible Increase of Guanidine in Blood of Certain Persons with Hypertension, *Arch Int Med* **40** 891 (Dec.) 1927.

40 Goldblatt, H., and Karsner, H. T. Site of Pressor Action of Dimethylguanidin Sulfate, *J Pharmacol & Exper Therap* **47** 247, 1933.

are shown in table 6.⁴¹ Because of the difficulty in obtaining sufficient material, only a few observations were made on cerebrospinal fluid. It is seen that the "guanidine" content of the blood is markedly increased and that appreciable quantities occur in the cerebrospinal fluid of dogs in the uremic state. Similar results have been obtained for patients with renal insufficiency (table 5).

The Significance of Guanidine in Uremia—Until more specific chemical methods demonstrate that the increased color reaction in uremic fluids is due to guanidine itself or to pharmacologically similar derivatives, it is not justifiable to assign this substance a definite rôle in the pathogenesis of the syndrome. That it may be important is suggested by the following facts: 1. Experimental guanidine intoxication produces vomiting, diarrhea, gastro-enteritis, muscular twitching, increases in

TABLE 6—*Studies of Guanidine Values for Uremic Dogs*

Number	Cause of Uremia	Mg per 100 Cc of Blood		Mg per 100 Cc of Cerebrospinal Fluid, Guanidine
		Nonprotein Nitrogen	Guanidine	
43	Ligation of renal arteries	200	1.76	
41	Ligation of renal arteries	73	0.61	
		130	0.76	
Hg2	Ligation of renal artery	211	5.80	
H7	Bilateral nephrectomy	158	3.45	
40B	Bilateral nephrectomy	176	5.60	
Hg5	Ligation of both ureters	113	2.50	
		254	5.88	
Hg1D	Ligation of both ureters	400	8.15	1.41
Hg1E	Nephrectomy	183	7.59	1.70
Hg10	Bilateral nephrectomy	176		Trace
Hg2B	Ligation of both ureters	153		0.43
73	Nephrectomy	45	1.01	

blood pressure and respiratory disturbances and in advanced stages apathy, stupor and circulatory collapse. These features are encountered also as a part of the symptom complex of uremia. 2. Guanidine behaves as the physiologic antagonist of calcium, and the nervous features of guanidine poisoning either in the intact animal or in the isolated muscle-nerve preparation can be inhibited by adequate amounts of calcium salts.⁴² Animals in a deficient state of nutrition in respect to calcium are more susceptible to guanidine intoxication, on the other hand, inten-

41 The "guanidine" content of the blood of normal dogs as determined by the Minot and Dodd method is usually less than 0.4 mg per hundred cubic centimeters, the spinal fluid containing no detectable amount. In analyses of fluids during uremia the color value of urea, uric acid and creatinine is compensated by adding similar amounts to the standard.

42 Minot, A. S., and Cutler, J. T. Guanidine Retention and Calcium Reserve as Antagonistic Factors in Carbon Tetrachloride and Chloroform Poisoning, *J. Clin. Investigation* 6:369, 1928. Kühnau, J., and Nothmann, M. Ueber die Guanidintoxikose und ihre Beziehungen zur Tetanie, *Ztschr. f. d. ges. exper. Med.* 44:505, 1924-1925.

sive calcium therapy will prevent the capillary damage, effects on carbohydrate metabolism and changes in blood pressure otherwise resulting from the administration of guanidine. 3 Salvesen⁴³ has pointed out that vomiting is usually the initial uremic symptom and may occur in persons without disturbances of the serum electrolytes and with only minimal elevations of the urea content of the blood, therefore at a time before any serious degree of gastro-intestinal irritation could be expected from the ammoniacal fermentation of urea—a mechanism suggested by Becher³ and supported by the experimental evidence of Hessel and Pekelis.⁴⁴ Vomiting is, however, an early feature of guanidine intoxication.

These facts support the hypothesis that guanidine may be responsible for the twitching observed in uremia when there is no evidence of "central" deficit of calcium ions. In the presence of a deficit the effects of guanidine are enhanced. It is further suggested that the early symptoms of gastro-intestinal irritation may be initiated and that the later symptoms of depression and collapse may be augmented by accumulation of this toxic organic base and/or its derivatives.

E THE RELATION OF UREA TO UREMIA

The available evidence (Fishberg²) indicates that the amounts of urea accumulating in body fluids in uremia are insufficient to induce a primary toxic action. Nevertheless, retention of urea may facilitate the development of the uremic state in several ways. 1 The effects of dehydration are augmented (Peters and Van Slyke¹⁹). 2 The osmotic pressure of bloody fluids is increased, a point stressed by von Korányi.⁴⁵ 3 Becher³ has claimed that bacterial decomposition of urea to ammonia in the alimentary tract is an important cause of stomatitis, gastritis and colitis. This hypothesis has been supported by Hessel and Pekelis,⁴⁴ who found that there was from 200 to 300 mg of ammonia per hundred cubic centimeters in the fluid from gastric fistulas of nephrectomized dogs and that when this material was constantly drained the damage to the mucosa of the tract below the fistula

43 Salvesen, H. A. Vomiting of Uremia and Its Relation to Pathochemical Blood Findings, *Acta med Scandinav* **81** 406, 1934.

44 Hessel, G., and Pekelis, E. Untersuchungen über die Ausscheidung harnfähiger Stoffe in den Magendarmkanal bei nephrektomierten Hunden. Ein Beitrag zur Frage der sog. vikariierenden Sekretion, Die Bedeutung der harnpflichtigen Stoffwechselschlacken in den Verdauungssaften für das Krankheitsbild und den Verlauf der Uramie. *Ztschr f d ges exper Med* **91** 331, 1933.

45 von Korányi, A. Physiologische und klinische Untersuchungen über den osmotischen Druck tierischer Flüssigkeiten, *Ztschr f klin Med* **33** 1, 1897. Klinische Thier, *ibid* **34** 1, 1898.

was in each case considerably less than it otherwise would have been. 4 Becher and also Fishbeig² have suggested that urea retention may inhibit the normal metabolism of precursors of urea, some of which may be toxic. This hypothesis has not, to our knowledge, been experimentally tested.

On the assumption that retention of urea might interfere with the normal rate of detoxication or decomposition of toxic substances, themselves not necessarily precursors of urea, we have observed the effects of elevation of the urea content of body fluids on the rate of disappearance of injected guanidine. A series of dogs were given equivalent doses of guanidine (25 mg per kilogram intravenously). A second series of dogs were given large intravenous injections of urea (2 Gm per kilogram) just prior to administration of guanidine. The "guanidine"

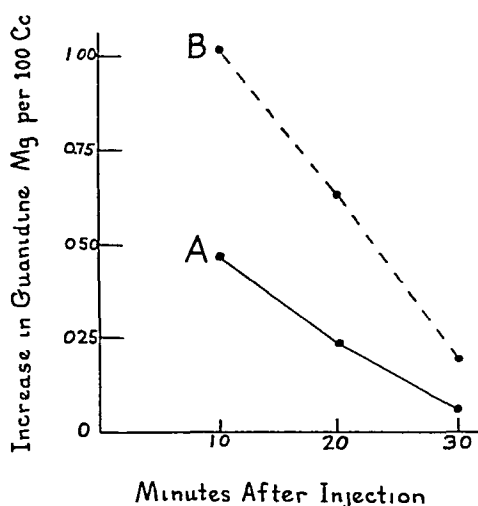


Chart 6—The procedure was exactly the same in all the animals except that one series (A) received guanidine only while the other group (B) were given urea also. The rate of disappearance from the blood of the injected guanidine was much slower in the latter animals. A, the average values for four dogs after the intravenous administration of 25 mg of guanidine hydrochloride per kilogram. B, the average values for four dogs after the administration of 25 mg of guanidine hydrochloride plus 2 Gm of urea per kilogram. This graph shows the retarding influence of urea on the disposal of injected guanidine in normal dogs.

content of the blood was then followed at intervals for thirty minutes. The results of these experiments (chart 6) indicate that the presence of urea delays the disappearance from the blood stream of administered guanidine. Little is known of the fate of injected guanidine. There is evidence, however, that some is excreted as such in the urine, some is transformed into creatine and some is destroyed by unknown paths. Which aspects of utilization of guanidine are interfered with by urea

cannot be stated, but it is unlikely that urinary excretion is hampered. It is felt that in renal insufficiency the elevation of blood urea may augment the accumulation of "guanidine" in body fluids⁴⁶

F DISTURBANCES IN ACID-BASE AND FLUID BALANCE OF BLOOD AND CEREBROSPINAL FLUID IN RELATION TO UREMIA

A good deal of evidence supports the conclusion that disturbances in acid-base and fluid balances in uremia are augmentatory influences which when present are of grave importance in respect to the condition of the uremic subject but which may be absent in spite of outspoken uremia. This point of view has been discussed in detail by Harrison and Mason.⁴

In a study of dogs with experimental uremia observations of the acid-base balance of serum and cerebrospinal fluid were made. It

TABLE 7—*Acid-Base Condition of Serum and Cerebrospinal Fluid of Dogs in Relation to Experimental Anuria*

Group	Arterial Serum			Cerebrospinal Fluid		
	pH	Carbon Dioxide Content, Vol %	Carbon Dioxide Tension, Mm of Mercury	pH	Carbon Dioxide Content, Vol %	Carbon Dioxide Tension, Mm of Mercury
Average values for four normal dogs	7.49*	50.4	30.1*	7.42	54.4	40.2
Average values for four dogs with anuria of three days' duration	7.38	26.7	20.2	7.40	55.3	46.3

* The low values for carbon dioxide tension and the high values for pH for the normal animals can probably be explained by the fact that the experiments were carried out in the summer and most of the animals were panting when samples were taken.

was noted that in dogs with rapidly developing renal insufficiency there was a surprising lag in the extension of the depletion of alkaline reserve, as indicated by findings in the serum and in the cerebrospinal fluid, and in the presence of severe uncompensated acidosis the findings in the cerebrospinal fluid were within normal limits. The results are given in table 7. Comparative studies of acid-base balance in serum and cerebrospinal fluid in states of renal insufficiency by others have produced contradictory results. The literature has been summarized by Katzenelbogen.⁴⁷

46 Observations were made on the effects of injections of the ethereal sulfate derivative of paracresol on the rate of disappearance of injected phenols from the blood stream. The results indicated that there was some diminution in the rate of disappearance of free phenol and paracresol under these conditions. Injections of urea with phenol or paracresol did not augment or diminish their toxicity. The effect of urea on the rate of disappearance of injected phenols was not studied.

47 Katzenelbogen, S. *The Cerebrospinal Fluid and Its Relation to the Blood*, Baltimore, Johns Hopkins Press, 1935.

G THE EFFECT OF UREMIC SERUM ON THE FROG HEART

Evidence of the multiplicity of factors which may play a rôle in the production of the uremic syndrome is obtained from a study of the effects of serum from dogs with renal insufficiency on the isolated frog heart used in the determination of ionized calcium by the method of McLean and Hastings¹³

The application of this method to the serum of normal dogs is hindered by augmentor effects which have no relation to the calcium ion concentration. Human serum, on the other hand, rarely is disturbing in this respect. The serum of dogs with experimental anuria of three or four days' duration commonly exerted one of two bizarre effects, aside from augmentation, on perfusion of the frog ventricle. In a number of instances diastolic arrest occurred promptly (chart 7). The substance

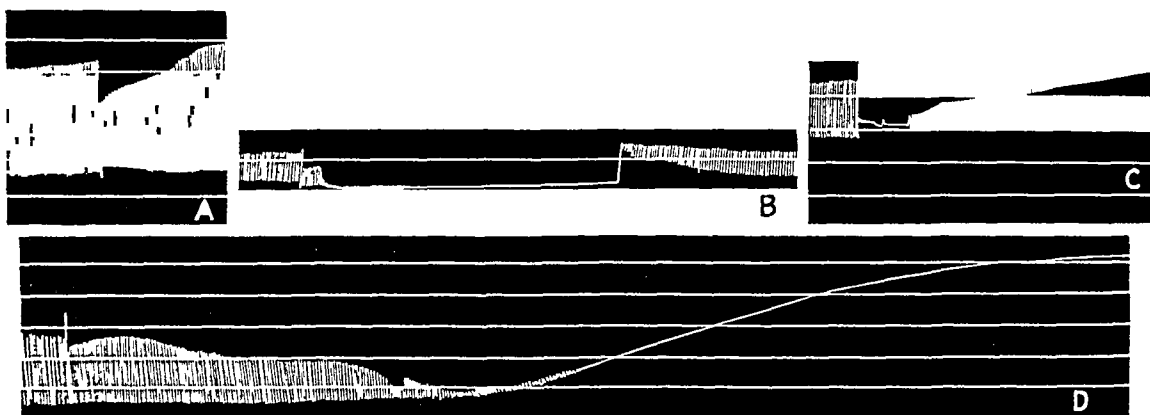


Chart 7—The records were obtained from the hearts of frogs, the upstrokes indicating systole. At the beginning of each curve the cannula in the heart contained Ringer's solution. Replacing this liquid with serum from uremic dogs caused several different effects: simple augmentation (A), diastolic arrest (B), which disappeared when the serum was replaced by Ringer's solution, and systolic arrest (C). The lower curve (D), illustrates all three effects from a single injection of serum.

responsible for this was found to be soluble in alcohol and ether and dialyzable. Phenol and paracresol added to the perfusion liquids were found to produce a similar effect. The most striking and common result was the production of systolic standstill (chart 7). This effect usually came on slowly, occasionally rapidly, and persisted for hours after replacement of the serum by the usual stock perfusion liquids. Although the ventricle was firmly contracted the auricle usually continued to beat. Attempts to study the chemical properties of the substance having this digitalis-like action were unsuccessful, largely because of the instability of the substance and the limitations of the frog heart method. It disappeared from serum in a few hours at room temperature and after a

day or two in the icebox. It was not recovered from serum ultrafiltrates. None of the commonly known substances retained in renal insufficiency had this effect. Whether this substance plays any rôle in the production of the uremic state in dogs cannot, of course, be stated. It is of interest that similar effects were occasionally produced also by serum from patients with uremia.

H CHANGE IN BLOOD PRESSURE IN RELATION TO UREMIA

Of twelve bilaterally nephrectomized animals, two displayed a rise in blood pressure, in nine of the remaining ten animals a diminution in blood pressure occurred some time after the operation. The increase,

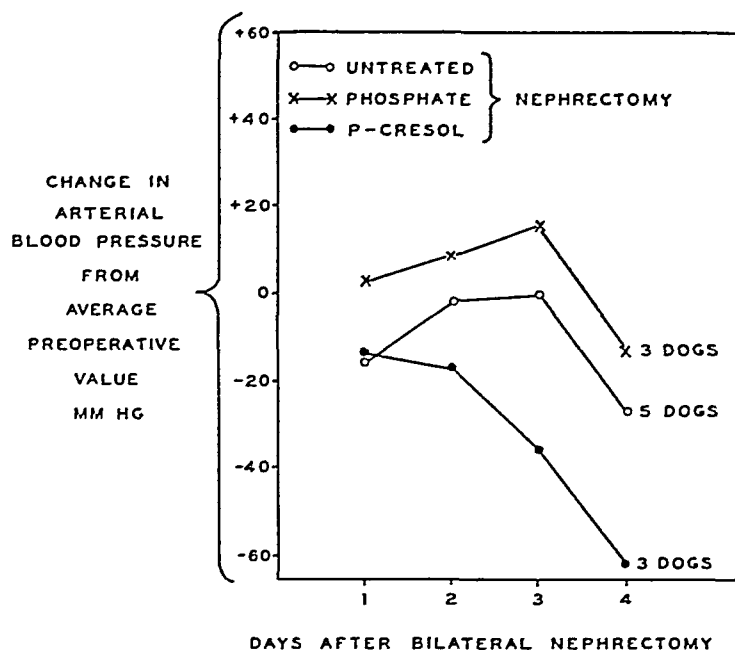


Chart 8—Each curve represents the average value for the blood pressure of three nephrectomized dogs. Those receiving daily injections of phosphate had the highest blood pressure, and those given paracresol the lowest, the untreated animals showing intermediate values.

when it occurred, was usually observed on the second or third post-operative day, while the most marked decline occurred after four or five days of anuria, when the animals were moribund. Since, as has been pointed out (chart 5), the intracisternal administration of phosphate causes a rise in blood pressure which can be prevented by the previous injection of free phenol, since guanidine intoxication may cause either an increase or a decrease in blood pressure, depending on the state of the animal and the dose of the compound, and since dehydration as the result of vomiting tends to cause a fall in blood pressure, it appears that the changes in the blood pressure in the anuric dog are the resultant of the interaction of several factors. Further evidence

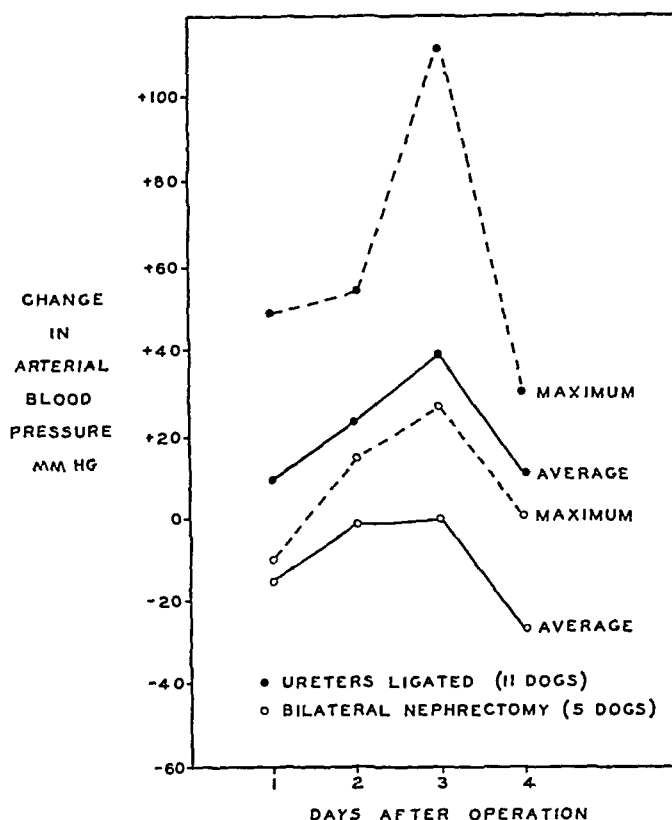


Chart 9—Maximal and average changes in blood pressure are compared in dogs subjected to double nephrectomy and those having both ureters ligated. The latter dogs tended to have hypertension, while the former usually displayed either no change or a decline in blood pressure.

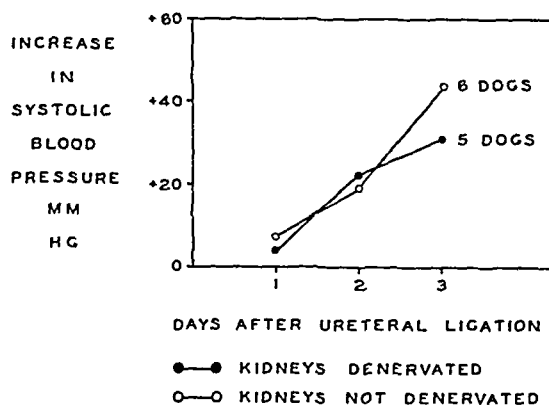


Chart 10—Denervation of the kidney had no significant effect on the rise in blood pressure produced by ligation of both ureters.

on this question was obtained by comparing the changes in blood pressure in three groups of nephrectomized animals, one group receiving daily intravenous injections of inorganic phosphate, a second receiving injections of phenol and the third being untreated. As shown in chart 8, the first group tended to have some increase in blood pressure, the second showed a well marked decline and the untreated nephrectomized animals showed an intermediate pressure.

After ligation of both ureters a distinct increase in blood pressure occurred in most of the animals on the second and third postoperative days. The degree of this change was variable, being as much as 100 mm in some dogs and not beyond the experimental error in others. On the average, however, these animals displayed a distinctly greater rise in blood pressure than did the nephrectomized dogs (chart 9). Since anuria was complete in both groups, the difference in response cannot be ascribed to retention products. In addition to the agents mentioned in the preceding paragraph, it appears that some other factor more specifically related to the presence in the body of abnormally functioning renal tissue must have been concerned in the production of the elevation in blood pressure following bilateral ureteral ligation. Such a pressor influence from the kidney might theoretically be exerted either by chemical or by "nervous," i.e., reflex, routes. The latter possibility is rendered unlikely by the fact that denervation of the kidneys had little or no effect on the rise in blood pressure produced by ureteral ligation (chart 10). Our experiments throw no light on the question as to whether this hypothetical chemical agent acts directly on the vessels or indirectly by way of the nervous system. In any case, it seems clear that while retention products may exert a slight influence in elevating the blood pressure, the chief factor in "renal" hypertension is some functional disturbance of the kidney other than that which leads to the accumulation of waste products in the body.

COMMENT

Numerous attempts to relate the symptoms of the uremic syndrome to accumulation of a single toxic substance have failed to receive clinical or experimental substantiation. These unitary theories of uremia have been discussed in detail elsewhere (Fishberg² and Harrison and Mason⁴). The available evidence indicates that the symptom complex is the summated expression of a number of interplaying factors, each of which in the last analysis is the result of the underlying disorder of function—failure to excrete the end-products of metabolism. Granting the incompleteness of the present knowledge, the experiments which have been described permit the drawing of certain generalizations concerning the mechanism of experimental uremia.

"Central" deficit of calcium ions appears to be an important cause of increased neuromuscular irritability. This deficit is brought about by accumulation of substances forming relatively unionized calcium salts. Retention of inorganic phosphate is important not only in this respect but also as a convenient indicator of the extent of the process. The fact already cited, that both in experimental phosphate intoxication and in experimental anuria twitching parallels the rise in inorganic phosphate and the fall in ionized calcium of the cerebrospinal fluid rather than similar changes in the serum, points to the nervous stimulation as being central rather than peripheral. In these dogs, as well as in patients with uremia, twitching is abolished by the intracisternal administration of calcium salts in amounts completely ineffective intravenously. The lag in development of changes in ionic pattern of the cerebrospinal fluid would probably be less marked in slowly developing renal insufficiency.

The same mechanism may play a minor rôle in the production of respiratory disturbances and of increase in blood pressure, both symptoms being produced by the intracisternal injection of phosphate, oxalate and citrate.

In many instances, however, twitching is absent in spite of evidence of "central" deficit of calcium ions or present when there is little evidence of such a deficit. Other mechanisms are therefore involved.

Accumulation of phenol derivatives appears to be an important factor in the production of weakness, apathy, stupor and coma, *i. e.*, the depressed phase of uremia. A rough parallelism exists between the amounts of these substances in the blood and the degree of apathy. Administration of free phenols to experimental animals produces stupor, administration to nephrectomized animals accelerates the development of weakness and apathy. In addition, the muscular twitching and increase in blood pressure arising from "central" deficit of calcium ions established by the intracisternal injection of phosphate may be completely inhibited by previous administration of phenol, either intravenously or intracisternally. It is believed, therefore, that when neuromuscular stimulation is absent, in spite of "central" deficiency of calcium ions, the inhibition is an expression of the pharmacologic action of retained phenols.

The uremic organism is to be thought of as being subjected to two major antagonistic influences—stimulation and depression. Additional factors, however, are concerned in this balance. Most of the important symptoms of uremia can be produced experimentally by guanidine intoxication, although the symptoms depend on the dose, route of administration and type and depth of anesthesia. It seems likely (although not proved conclusively) that the "guanidine" accumulating in body fluids during uremia is guanidine and/or its derivatives. It is

inferred, therefore, that guanidine, the physiologic antagonist of calcium, may be responsible for increased neuromuscular irritability in those instances in which there is no evidence of calcium ion deficit. On the other hand, extreme degrees of guanidine accumulation may well augment the symptoms of apathy and stupor, such as occasionally occur with minimal phenol retention. Guanidine probably plays a part also in the development of vomiting, diarrhea and gastro-enteritis occurring in the uremic state.

The "nervous" manifestations of uremia are, then, to be thought of as resultants of two opposing influences. "Central" deficit of calcium ions tends to cause irritative phenomena, whereas accumulation of phenol derivatives favors exhibition of apathy, weakness and stupor. The clinical picture depends on which is in ascendancy, and accordingly one may observe twitching and convulsions or weakness and stupor or alternations and combinations of these states. This balance is further complicated by the influence of "guanidine" bodies which, depending on conditions, may produce either manifestations of irritation or depression.

The available evidence indicates that retention of urea, the cardinal sign of renal insufficiency, is only indirectly embarrassing to the organism. Ammonium salts, formed by bacterial decomposition of urea in the alimentary tract, augment gastro-intestinal irritation. Evidence has been discussed indicating that high concentrations of urea interfere with the disposal of guanidine by the body.

The increase in blood pressure often encountered in experimental uremia may be brought about in part by overactivity of the medullary centers as a result of deficiency of calcium ions⁴⁸. This mechanism ordinarily is of little import, and the hypertension is related to the presence in the organism of abnormally functioning renal tissue rather than to retention of normal urinary constituents. This view is supported by the observations showing that bilateral ureteral ligation in dogs produces a greater and more constant hypertension than does bilateral nephrectomy.

Some evidence has been gained that accumulation of conjugated phenols inhibits the further detoxication of free phenols. Further investigations of the detoxifying functions of the kidney, liver and gastro-intestinal canal in states of renal insufficiency are needed. It is possible that the similarities between the clinical picture of advanced hepatic insufficiency and the depressed phase of uremia may be consequences of the same mechanism—failure to detoxify or otherwise dis-

48 Patients in whom uremia develops frequently display a slight or moderate increase in blood pressure (usually superimposed on already existing hypertension) not referable to the onset of congestive heart failure. Intracisternal injections of calcium salts in several instances abolished this increment of hypertension.

pose of certain poisonous products of the intermediary metabolism of tissues or bacterial action in the intestines

The factors which have been mentioned are probably not the only ones responsible for the uremic syndrome and many still unknown influences may be operative. In certain instances dehydration greatly increased protein catabolism and base and chloride deficit, with acidosis, appear to be of no little import, however, while these disturbances often augment the development of uremia, they are not essential features of the symptom complex, and all may be absent in occasional instances

SUMMARY

The uremic syndrome produced in dogs by bilateral nephrectomy resembles that brought about by ligation of both ureters except that a rise in blood pressure is more likely to follow the latter procedure

The manifestations of increased neuromuscular irritability of anuric dogs are believed to be dependent on the retention of substances having an antagonistic action—either chemically or pharmacologically—to ionized calcium. Since these manifestations tend to parallel the deficit of calcium ions in the cerebrospinal fluid rather than that in the serum, it is believed that they are mediated centrally

The depressed phenomena of uremia are ascribed to the retention of phenolic bodies

Variations in the nervous manifestations of anuric dogs are believed to be dependent on the balance between opposing factors—those tending to produce irritative phenomena and those leading toward depression

Investigations of the guanidine content of the body fluids of uremic organisms and studies of experimental guanidine intoxication indicate that this compound may play an important rôle in the production of some of the clinical features of the syndrome

Data have been presented which indicate that disturbance of acid-base balance, retention of urea and accumulation of substances as yet unidentified also play a rôle

On the basis of these observations a hypothesis has been outlined which accounts for the chief features of the uremic syndrome

Progress in Internal Medicine

INFECTIOUS DISEASES

REVIEW OF CURRENT LITERATURE

HOBART A. REIMANN, M.D.

PHILADELPHIA

Notable advances of academic and practical value have been reported during the past year, especially with regard to the more common infections. A new form of antipneumococcus serum has been proposed, and, according to reports, chemotherapy in certain streptococcal and colon bacillus infections has at last attained a modicum of success. Information in regard to the etiology of influenza has been clarified, and further advances have been made in the highly important field of the "crystalline viruses."

PNEUMONIA

Judging from the number of studies published during the past year, recognition of the importance of regarding pneumonia from an etiologic point of view, as advocated for more than twenty years by Cole, has finally become general. The subject is excellently reviewed by Cole¹ in several articles. Further evidence of the interest in this most important of infectious diseases is the organization of special campaigns or commissions for its study and control in many states and cities, lately in Pennsylvania, Minnesota, Ohio and Maryland. The plan of the campaign in the state of New York is outlined by Rogers². During the past year a number of important papers have appeared on the treatment with specific serum of pneumonia caused by various types of pneumococci.

Type I Infections—Cecil³ points out that all the recent reports dealing with the therapeutic effectiveness of Felton's concentrated serum without exception have been favorable. He reemphasizes the impor-

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1 Cole, R. Recent Advances in the Control of Pneumonia, *Am J Pub Health* **26** 1191-1197 (Dec.) 1936, The Treatment of Pneumonia, *Ann Int Med* **10** 1-13 (July) 1936, Pneumonia, *New York State J Med* **36** 1699-1709 (Nov. 15) 1936.

2 Rogers, E. S. The New York State Program for the Control of Pneumococcus Pneumonia, *Am J Pub Health* **27** 133-141 (Feb.) 1937.

3 Cecil, R. L. Effects of Very Early Serum Treatment in Pneumococcus Type I Pneumonia, *J A M A* **108** 689-692 (Feb. 27) 1937.

tance of giving specific antiserum early in the illness. The disease may in fact be completely aborted if treated early enough, as I have also noted in my own experience. Cecil collected reports of 160 cases in which treatment was given in the first twenty-four hours of illness. Only 8 deaths occurred, making a remarkably low mortality rate of 5 per cent, as compared with from 20 to 25 per cent in cases in which treatment with serum was not given. No complications occurred in his series of 37 cases. Benjamin, Blankenhorn and Senior⁴ in 50 cases of infection due to type I pneumococci gave treatment early in the disease, and in no case did death occur. Abernethy⁵ reports 25 consecutive cases in which serum was given, with no deaths and no serious complications. He found it possible to regulate the dose of serum by use of the cutaneous test with type I polysaccharide. The average number of units given was 335,000. About 200,000 units was necessary in the average case in which there was no complication. Finland⁶ found that 75,000 units was adequate early in the disease, but he recommends giving 150,000 units when more than one lobe is involved and 250,000 or more units if culture of the blood gives a positive result. He found the most frequent causes for failure of serum treatment to be (a) error in typing, (b) insufficient doses or spread of doses over too long an interval, (c) beginning focal complication, (d) mixed infection in the lungs, (e) other complicating factors and diseases, (f) errors in estimating the time of onset of the disease and (g) the extent of the pulmonary lesion. Another analysis⁷ of failure of serum treatment in 44 cases shows that the chief causes were (a) the advanced age of the patient, (b) the delay in giving serum, (c) the inadequate doses of serum, (d) the severe anoxemia and (e) the presence of complications or other diseases.

The mortality rate for rats infected with type I pneumococci was reduced by treatment with sulfanilamide^{7a}. Clinical tests made elsewhere, but not reported on as yet, were disappointing.

4 Benjamin, J. E., Blankenhorn, M., and Senior, F. A. The Results of the Treatment of Pneumonia with Specific Therapeutic Serum, *Ohio State M J* **33** 36-42 (Jan.) 1937.

5 Abernethy, T. J. Concentrated Antipneumococcus Serum in Type I Pneumonia, *New York State J Med* **36** 627-635 (April 15) 1936.

6 Finland, M. Adequate Dosage in the Specific Serum Treatment of Pneumococcus Type I Pneumonia, *Am J M Sc* **192** 849-865 (Dec.) 1936.

7 Rosenbluth, M. B., and Block, M. Pneumonia Due to Type I Pneumococcus, *Arch Int Med* **58** 102-116 (July) 1936.

7a Gross, P., and Cooper, F. B. *P*-Aminobenzenesulfonamide and Antipneumococcal Serum Therapy in Type I Pneumococcal Infection of Rats, *Proc Soc Exper Biol & Med* **36** 535-540 (May) 1937.

Type II Infections—Two epidemiological studies involving type II pneumococci are reported. In one⁸ an epidemic was traced through healthy carriers from one winter to the next, when a new outbreak occurred centering about these carriers. In none of the carriers did pneumonia develop, but apparently they transmitted the infection to susceptible persons, who then contracted the disease. A specific vaccine used prophylactically seemed to check the spread.

The other report⁹ concerns the development of type II pneumonia in 9 persons after an epidemic of infection of the respiratory tract in a camp. Nineteen per cent of the members of the camp were found to be carriers of this pneumococcus. Fifteen weeks later carriers of type II pneumococci were still present. No cases of pneumonia occurred in a similar camp in a different county in which a similar epidemic of infection of the respiratory tract occurred. These studies emphasize the importance of carriers in the transmission of pneumonia and what advances may be made in the understanding and control of epidemics when infectious diseases are regarded from an etiologic point of view.

Type III Infections—A new mode of attack on type III infection is suggested by observations from two laboratories. It is a well known fact that most strains of type III pneumococci are avirulent for rabbits. Enders and Shaffer¹⁰ attempted to discover the characteristics of certain strains of type III pneumococci on which depend survival or destruction of the organisms when they are injected into the rabbit. They subjected pneumococci of numerous strains to a temperature of 41 C and found that the majority failed to grow. This suggested a possible relationship to the avirulence of type III pneumococci for rabbits, since the temperature of these animals was found to rise even higher than 41 C after intravenous injection. After further trial they found that strains of pneumococci which grew at 41 C were the only ones which were virulent for rabbits. Their work suggests that the rise in temperature following inoculation may be the most important factor in the natural resistance of the rabbit to certain strains of pneumococci. Further experiments by these investigators showed that not all "thermo-resistant" strains are virulent. Other factors also exist,

8 Smilie, W. G. A Study of an Outbreak of Type II Pneumococcus Pneumonia in the Veterans' Administration Hospital at Bedford, Massachusetts, *Am J Hyg* **24** 522-535 (Nov.) 1936.

9 Harris, A. H., and Ingraham, H. S. A Study of the Carrier Condition Associated with Type II Pneumonia in a Camp of the Civilian Conservation Corps, *J Clin Investigation* **16** 41-48 (Jan.) 1937.

10 Enders, J. F., and Shaffer, M. F. Studies on Natural Immunity to Pneumococcus Type III, *J Exper Med* **64** 7-18 (July) 1936. Enders, J. F., Wu, C. J., and Shaffer, M. F. Studies on Natural Immunity to Pneumococcus Type III, *ibid* **64** 425-438 (Sept.) 1936.

such as the size of the capsule and the ease with which it is destroyed by humoral influences. Similar results, though derived from a different mode of attack, are reported by Rich and McKee¹¹. They found that within twenty-four hours after injection of type III pneumococci rabbits become highly resistant to a second injection of similar organisms. Since this interval is too short to account for the development of specific immunity, the authors conclude that the fever which developed shortly after the first injection prevented growth of type III pneumococci, which cannot grow at similar high temperature in vitro. Under these conditions the cocci gradually lose their capsules and become subject to phagocytosis, or they may die without being taken up by cells. Phagocytosis in itself does not appear to be important. The results of both of these studies suggest the use of fever therapy in the treatment of human beings with infections due to type III pneumococci.

Experiments with antipneumococcus serum obtained from rabbits are being made with regard to the treatment of type III pneumonia. The subject is discussed in a subsequent paragraph.

Several studies have been made concerning the effectiveness of sulfanilamide in prolonging and saving the lives of mice¹² and rats¹³ experimentally infected with type III pneumococci. Sulfanilamide was administered also to 13 patients¹⁴ with type III pneumonia, 9 of whom recovered, in contrast with 10 patients who were not given the drug, 8 of whom died. The results are suggestive, but until a much larger series has been studied the clinical value of the drug cannot be appraised. The small number of cases should not give rise to false hopes and indiscriminate use of the drug to the exclusion of known and proved methods.

Type V Infections—Finland and Tilghman¹⁵ found that in 26 per cent of cases pneumonia caused by the type V pneumococcus was atypical clinically, in contrast with 4 per cent of those caused by the serologically related type II pneumococcus. There were also more

11 Rich, A. R., and McKee, C. M. The Mechanism of a Hitherto Unexplained Form of Native Immunity to the Type III Pneumococcus, *Bull. Johns Hopkins Hosp.* **59** 171-207 (Sept.) 1936.

12 Rosenthal, S. M. Studies in Chemotherapy. Chemotherapy of Experimental Pneumococcus Infections, *Pub. Health Rep.* **52** 48-53 (Jan. 8) 1937.

13 Gross, P., and Cooper, F. B. Efficacy of *p*-Aminobenzenesulfonamide in Experimental Type III Pneumococcus Pneumonia of Rats, *Proc. Soc. Exper. Biol. & Med.* **36** 225-227 (March) 1937.

14 Heintzelman, J. H. L., Hadley, P. B., and Mellon, R. R. The Use of *p*-Aminobenzenesulphonamide in Type III Pneumococcus Pneumonia, *Am. J. M. Sc.* **193** 759-763 (June) 1937.

15 Finland, M., and Tilghman, R. C. Clinical and Immunologic Observation in Cases of Pneumococcus Type V Pneumonia Treated with Specific Antibody, *New England J. Med.* **215** 1211-1221 (Dec. 24) 1936.

purulent complications in the cases of type V pneumonia than in those of pneumonia caused by the type II pneumococcus. They report the results obtained in 26 cases of type V pneumonia with specific anti-serum, which was found to be a useful agent when given in adequate amounts early in the disease. The mortality rate in a series of 197 cases in which serum was not given was about 45 per cent, as compared with 15 per cent in 26 cases in which serum was given. Bullowa and Wilcox¹⁶ report similar favorable results.

Barnes and Wight¹⁷ raise the important academic question of the possible spontaneous transformation of type V into type II pneumococci.

Type VII Infections—A study¹⁸ of 160 cases of pneumonia caused by the type VII pneumococcus was made. The type VII pneumococcus also was encountered in numerous conditions other than pneumonia, as for example in meningitis, otitis media, peritonitis and various infections of the upper respiratory tract. In most of the cases the pneumonia was of the lobar form, but in about 20 per cent it was atypical. In 63 per cent of the cases pneumonia was preceded by some other infection of the respiratory tract. In only 22 per cent of the cases did the disease terminate favorably before the sixth day. In a series of 30 cases in which serum was given, the disease ended before the sixth day in 84 per cent of the cases in which recovery was obtained. The mortality rate in 130 cases in which serum was not given was 38 per cent, as compared with 10 per cent in 30 cases in which serum was given. Doses of from 80,000 to 100,000 units appeared to be adequate in cases of uncomplicated pneumonia. Twice the amount is advocated when bacteremia exists.

Type XIV Infections—In a paper by Moor and Brown¹⁹ one reads the amazing report that pneumococci were found in the urine of 30 per cent of 329 persons with infection of the genito-urinary tract, moreover, all of the 27 cultures which were "typed" showed type XIV pneumococci. These findings are so different from the reports of all previous observers that an immediate checking of the results is impera-

16 Bullowa, J. G. M., and Wilcox, C. Therapeutic Serum of Pneumococcus Type V (Cooper) Pneumonia, *J. Clin. Investigation* **15** 711-715 (Nov.) 1936.

17 Barnes, L. A., and Wight, E. C. Spontaneous Transformation of Pneumococcus Type V to Type II, *J. Bact.* **32** 557-566 (Nov.) 1936.

18 Finland, M., Ruegsegger, J. M., Dowling, H. F., and Tilghman, R. C. Infections with Pneumococcus Type VII, *Am. J. M. Sc.* **193** 48-59 (Jan.) 1937. Finland, M., Tilghman, R. C., Ruegsegger, J. M., and Dowling, H. F. Clinical and Immunological Observations, *ibid.* **193** 59-81 (Jan.) 1937.

19 Moor, H. D., and Brown, I. D. The Occurrence of Diplococcus Pneumoniae in Infections of the Urinary Tract, *J. A. M. A.* **108** 1594-1596 (May) 8) 1937, abstr., *J. Bact.* **33** 73-74 (Jan.) 1937.

tive It would be of interest to learn whether the type XIV pneumococcus is especially fitted to produce disease of the urinary tract, in a manner similar to that of the type II pneumococcus, which appears at times to have a special predilection for the endocardium

Pneumonia in Infants and Children—Bullowa and Greenbaum²⁰ studied pneumonia in 539 children, the majority of whom were under 6 years of age Among infants under 2 years of age, type XIV pneumococci caused 18 per cent of the cases, type VI, 13 per cent, type XIX, 7 per cent, and type I, only 5 per cent In patients over 2 years of age type I infections were dominant (24 per cent), with type XIV next in importance (13 per cent) Pneumococci of types V, VI, IV, III and VII were next in order of frequency Pneumococcic pneumonia is three times as fatal in children less than 2 years old as in older children Pneumonia which assumes the atypical or bronchial form is twice as fatal as the lobar form, regardless of the type of the pneumococcus

Nemir and her associates²¹ studied 1,033 cases of pneumonia in children and found that in 42 per cent the condition was associated with pneumococci of types I, VI and XIV The type I pneumococcus was rarely found in infants under 2 years of age, while type XIX almost always occurred in children of this age Type XIX and type VI occurred most often in those who did not have pneumonia, in contrast with type I and type XIV, which were rarely obtained from this group Type I and type V pneumococci produced empyema in 39 per cent of the cases in which this complication developed The highest death rate occurred among infants under 2 with atypical pneumonia or bronchopneumonia and in those with streptococcic and staphylococcic pneumonia The mortality rate for patients with bronchopneumonia was 50 per cent, and that for patients with the lobar form was only 5 per cent Specific serum therapy was most effective against infections caused by pneumococci of types I, XIV, V and VII

Endemic Pneumonia—Bullowa and Wilcox²² made a survey of 4,048 cases of pneumonia noted during a seven year period to determine the incidence of various types of pneumococci involved Similar surveys were made by Gundel several years ago There were distinct differences from year to year and from month to month It was noted,

20 Bullowa, J G M, and Greenbaum, E Pneumococcic Pneumonia in Infants and in Children, *Am J Dis Child* **53** 22-31 (Jan) 1937

21 Nemir, R L, Andrews, E T, and Vinograd, J Pneumonia in Infants and in Children, *Am J Dis Child* **51** 1277-1295 (June) 1936

22 Bullowa, J G M, and Wilcox, C Endemic Pneumonia Pneumococcic Types and Their Variations in Incidence and Mortality for Adults and Children, *Arch Int Med* **59** 394-407 (March) 1937

for example, that when the number of cases of type I pneumonia increased, the number of cases of type II pneumonia decreased. Type III and type VIII infections were more prevalent during the last two years than in the five preceding ones. Type V infection was prevalent in 1930, the incidence diminished and then increased to a new high level in 1934. Type VIII infections were prevalent all through the pneumonia season of 1934 to 1935, type I infections in January and February and type V pneumonia in April and May.

Finland²³ summarizes his studies of 3,682 cases in which the type of pneumonia was determined. The reader is referred to this paper for a statistical analysis and tabulation of many important features in regard to types of pneumococci.

Antipneumococcus Serum—It appears that a distinct advance has been made by the substitution of rabbit serum for horse serum in the treatment of pneumonia. Goodner, Horsfall and Bauer²⁴ found considerable difference in the size, solubility and degree of specificity of the antibodies of serum from these species of animals. Some advantages of rabbit serum are as follows: 1. The potency is greater, as indicated by higher protection conferred on mice. 2. The smallness of the antibody permits greater diffusion of the serum. Immune bodies after intravenous injection have been demonstrated in empyema fluid. 3. The cost of preparing rabbit serum is less than that of preparing horse serum. 4. Unconcentrated rabbit serum is approximately as potent as concentrated horse serum. Methods are being developed for the refinement and concentration of rabbit serum. The results of the treatment of patients with antipneumococcus rabbit serum have been encouraging. Because of the small size of the protein molecule it is hoped that rabbit serum is more penetrative of serous membranes than horse serum and that it will favorably influence empyema, meningitis and other focal complications. Preliminary studies give encouragement, at least as far as empyema is concerned. Twenty-two patients were treated with rabbit serum, with no deaths from pneumonia²⁵. In several cases the patient had an infected pleural exudate, which disappeared without thoracotomy—a notable fact. In my own experience the therapeutic response to rabbit serum has been favorable in pneu-

23 Finland, M. The Significance of Specific Pneumococcus Types in Disease, Including Types IV to XXXII (Cooper), *Ann Int Med* **10** 1531-1543 (April) 1937.

24 Goodner, K., Horsfall, F. L., and Bauer, J. H. Ultrafiltration of Type I Antipneumococcal Sera, *Proc Soc Exper Biol & Med* **34** 617-619 (June) 1936.

25 Horsfall, F. L., Goodner, K., MacLeod, C. M., and Harris, A. H. Type Specific Antipneumococcus Rabbit Serum, *Science* **84** 579-581 (Dec 25) 1936, Antipneumococcus Rabbit Serum as a Therapeutic Agent in Lobar Pneumonia, *J A M A* **108** 1483-1490 (May 1) 1937.

monia caused by pneumococci of types III, IV, V, VII and XIV, but immediate or delayed reactions frequently occurred, indicating that further work must be done in refining the serum

One company manufacturing biologic products has purchased 7,000 rabbits for making antipneumococcus serum and will probably place antiserums for all thirty-two types of pneumococci on the market next winter

A study²⁶ is reported in which it is shown that the intravenous injection of serum is the method of choice, since a greater and more constant concentration is attained and the effects appear more rapidly and persist longer than when serum is given by the intramuscular or the subcutaneous route. Untoward reactions to initial injections were less frequent when serum was injected intramuscularly, which may be of practical importance in treating patients who are sensitive to serum

Felton²⁷ marshals evidence to prove that pneumococcus antibodies found in horse serum are of protein nature. Chow and Wu²⁸ arrived at similar conclusions by isolating "immunologically pure antibody." They suggest the possibility of preparing potent antiserums for certain types of infection heretofore resistant to specific therapy, especially for type III pneumonia. By ultracentrifugation Wyckoff²⁹ succeeded in precipitating and concentrating immune bodies of type I antipneumococcus serum. The protein molecules found in the bottom layers had definite and constant physical characteristics. Protein molecules of similar nature were found in antiserum prepared with other types of pneumococci but not in normal horse serum. This precipitable globulin is perhaps made or freed in excess during the process of immunization. It was also found that the protein content was not increased in antipneumococcus serum containing both type I and type II antibodies, which indicates that a single globulin molecule can exhibit the characteristics of more than one antibody

Miscellaneous—In an epidemiological study Tilghman and Finland³⁰ present thirty-three groups of multiple cases of pneumococci

26 Tilghman, R. C., and Finland, M. The Availability of Specific Pneumococcus Antibody After Intravenous, Intramuscular and Subcutaneous Injection, *J Immunol* **31** 239-255 (Sept.) 1936

27 Felton, L. Pneumococcus Antibodies—What Are They? *Science* **79** 277-278 (March 23) 1934

28 Chow, B. F., and Wu, H. Isolation of Immunologically Pure Antibody, *Science* **84** 314 (Oct. 2) 1936

29 Wyckoff, R. W. G. The Ultracentrifugal Concentration of Pneumococcus Antibodies, *Science* **84** 291-293 (Sept. 25) 1936

30 Tilghman, R. C., and Finland, M. Pneumococcus Infections in Families, *J Clin Investigation* **15** 493-499 (Sept.) 1936. Finland, M., and Tilghman, R. C. Bacteriological and Immunologic Studies in Families with Pneumococcus Infections *ibid* **15** 501-509 (Sept.) 1936

infection apparently contracted directly from patients with the same type of infection. Most of the infections involved type I and type II pneumococci. In some instances the contracted infection appeared as lobar pneumonia, in others, as empyema, meningitis, otitis media or bronchopneumonia. A high incidence of carriers was noted in families in which various members had the infection. Serologic studies showed that homologous type-specific antibodies may appear in the blood of healthy contact carriers. Killian³¹ believes that a hereditary familial disposition of susceptibility to pneumonia is present. This may be so, but one wonders if the examples of family infection which he cites are not simply the result of infections due to contact with carriers. A report³² of experiments and observations in support of the value of artificial pneumothorax in the treatment of pneumonia has been published.

Numbers of cases of staphylococcic pneumonia, especially in children, are reported³³ which confirm my view in regarding this infection as a disease entity. Streptococcic septicemia³⁴ was discovered in 8 cases of pneumococcic pneumonia as a late complication or sequela. A review³⁵ of the literature and a study of pneumonia caused by Friedlander's bacillus was made. The records of 32 patients were studied, mostly persons in late middle life. The onset of pneumonia was usually abrupt, and the course was without any special clinical characteristics, except that the sputum, which was usually a thick mixture of mucus and blood, brick red and homogeneous contained a predominance of capsulated gram-negative bacilli. Only one type of Friedlander's bacillus was isolated, namely, type A of Julianelle. Septicemia was present in 19 of 27 cases. There was a tendency to absolute or relative leukopenia. In about half the cases typical signs of consolidation were absent. Gross abscess formation was the most frequent complication, empyema and meningitis were less common. Specific antiserum was tested therapeutically, and no beneficial effect was noted.

31 Killian, H. Zur Frage der Disposition zur Pneumokokkenerkrankungen der Lunge, *Klin Wchnschr* **15** 1469-1471 (Oct 10) 1936

32 Kaltreider, N. L., Hyde, H. V., and Fray, W. W. Pulmonary Capacity in Lobar Pneumonia, with Special Reference to Collapse Therapy, *Arch Int Med* **59** 408-431 (March) 1937

33 Troisier, J., Bariety, M., and Brocard, H. La staphylococcie pleuro-pulmonaire primitive, *Ann de med* **39** 189-210 (Feb) 1936. MacGregor, A. R. Staphylococcal Pneumonia, *Arch Dis Childhood* **11** 195-205 (Aug) 1936. Conklin C. B. Sporadic Outbreak of Neonatal Pneumonia, *M Ann District of Columbia* **5** 264-269 (Sept) 1936

34 Solomon, S., and Curphey, T. J. Streptococcic Septicemia Complicating Pneumococcic Lobar Pneumonia, *J A M A* **108** 187-193 (Jan 16) 1937

35 Solomon, S. Primary Friedlander Pneumonia, *J A M A* **108** 937-947 (March 20) 1937

Thirty-one of the 32 patients died. Collins³⁶ reports a case of pneumonia due to Friedlander's bacillus and calls attention to the existence of chronic pulmonary disease caused by this organism which may easily be mistaken for tuberculosis unless the causative organism is identified.

INFLUENZA

A number of studies have confirmed and extended the highly important work on the etiology of influenza. In further investigation of the theory that the epidemic of swine influenza in 1918 was caused by the same virus which caused influenza in human beings at the same time, Shope³⁷ measured the neutralizing antibodies of the serum of persons of different ages. He showed that the serum of many adults who survived the pandemic of 1918 contained antibodies which neutralized the virus recently obtained from swine, whereas the serum from children born after 1918 did not. The results suggest that the virus in swine has persisted as such and that young persons who were not in contact with the virus of the pandemic therefore do not have neutralizing bodies in their serum. The same author³⁸ reviews the subject in a monograph. Francis and Magill³⁹ demonstrated protective antibodies for a strain of human influenza virus in about half of the persons over 1 year of age who were tested. A much higher percentage of serums of persons recently convalescent from influenza showed completely protective effects when tested on mice into which virus was injected. Virus neutralization tests were found to be accurate in determining early influenzal infection.⁴⁰ Human and swine viruses contain certain antigenic components in common. The same investigators⁴¹ confirmed Elkele's work and succeeded in infecting pigs with virus derived from human beings. The disease caused by the human virus was less severe than that which followed experimental infection with swine virus in these animals, which indicates that the two strains

36 Collins, L. H. Chronic Pulmonary Infection Due to the Friedlander Bacillus, *Arch Int Med* **58** 235-249 (Aug.) 1936

37 Shope, R. E. The Incidence of Neutralizing Antibodies for Swine Influenza Virus in the Sera of Human Beings of Different Ages, *J Exper Med* **63** 669-684 (May) 1936

38 Shope, R. E. Influenza of Swine and Man, *Medicine* **15** 453-487 (Dec) 1936

39 Francis, T., and Magill, T. P. The Incidence of Neutralizing Antibodies for Human Influenza Virus in the Serum of Human Individuals of Different Ages, *J Exper Med* **63** 655-668 (May) 1936

40 Francis, T., and Shope, R. E. Neutralization Tests with Sera of Convalescent or Immunized Animals and the Viruses of Swine and Human Influenza, *J Exper Med* **63** 645-653 (May) 1936

41 Shope, R. E., and Francis, T. The Susceptibility of Swine to the Virus of Human Influenza, *J Exper Med* **64** 791-801 (Nov) 1936

are similar but not identical. Serial passage of human virus through swine did not enhance its virulence or change it immunologically. Further studies indicated some antigenic differences between certain strains derived from human sources which were previously thought to be identical.⁴²

Practical application of the advances in knowledge has recently been made. Stokes and his associates⁴³ vaccinated about 250 persons in a large colony before an epidemic of influenza broke out which affected about 25 per cent of the group. Vaccine was made from virus obtained from both swine and human sources and grown in tissue culture, and from a 10 per cent emulsion of infected mouse lung in physiologic solution of sodium chloride. The emulsion was filtered and injected intramuscularly in doses of 0.5, 1 and 1 cc, respectively, at weekly intervals. The results of the vaccinations were as follows. In 12.5 per cent of 550 unvaccinated persons febrile infections developed, a similar percentage of those vaccinated with swine virus became ill, but in only 2.7 per cent of those vaccinated with human strains of virus did febrile disease develop. In all three groups the vaccine had no influence on the development of afebrile symptoms regarded as those of the common cold.

Stokes noted that persons who possessed virus-neutralizing bodies in their serum were still susceptible to the disease. It appears that as in other diseases, notably poliomyelitis, resistance to infection and neutralizing properties of the serum are associated but not always parallel. Similar observations were made by English investigators,⁴⁴ who also claim that the complement fixation test provides a possible method for differentiating immune from susceptible persons. By means of the test a high antibody titer was generally found in convalescent serum.

Two Russian investigators⁴⁵ sprayed cultures of Pfeiffer's bacillus (*Haemophilus influenzae*) into the respiratory tracts of 110 volunteers.

42 Magill, T. P., and Francis, T. Antigenic Differences in Strains of Human Influenza Virus, *Proc Soc Exper Biol & Med* **35** 463-466 (Dec.) 1936. Francis, T. Epidemiological Studies in Influenza, *Am J Pub Health* **27** 211-225 (March) 1937.

43 Stokes, J., Chenoweth, A. D., Waltz, A. D., Gladen, R. G., and Shaw, D. Results of Immunization by Means of Active Virus of Human Influenza, *J Clin Investigation* **16** 237-243 (March) 1937.

44 Hoyle, L., and Fairbrother, R. W. Isolation of the Influenza Virus and the Relation of Antibodies to Immunity, *Brit M J* **2** 655-657 (March 27) 1937.

45 Smorodintseff, A. A., Drobyshevskaya, A. I., Ostrovskaya, S. M., and Shishkina, O. I. Clinical and Laboratory Investigation on Volunteers Infected with Pfeiffer's Bacillus, *Lancet* **2** 1381-1383 (Dec 12) 1936. Smorodintseff, A. A., Drobyshevskaya, A. I., and Shishkina, A. O. On Etiology of the 1936 Influenza Epidemic in Leningrad, *ibid* **2** 1383-1385 (Dec 12) 1936.

All the subjects became ill within from four to six hours but fortunately recovered in a day or two. The symptoms did not resemble those of grip or influenza, and leukocytosis was present in all. Contagion did not occur. The results proved the pathogenicity of Pfeiffer's bacillus, but the disease caused thereby did not resemble influenza. The same investigators isolated a filtrable virus from patients with influenza which was identical with the strains of the virus isolated in England.

Brightman and Trask⁴⁶ show how difficult it is to differentiate influenza from the common cold on a clinical basis. They believe it possible to make a definite diagnosis of influenza by producing symptoms in ferrets inoculated intranasally with nasopharyngeal secretions from the patients. Ferrets do not become ill when inoculated with secretion from normal persons or from those suffering from the common cold. The strain of influenza virus they isolated was immunologically similar to strains isolated by others from widely scattered sources.

Interesting observations made by Wells and Brown on the recovery of the virus of influenza from the air will be discussed in a later paragraph.

STREPTOCOCCIC INFECTIONS

Chemotherapy—A great deal of attention has been focused on recent developments in chemotherapy. Interest has centered especially on the enthusiastic support given to the use of sulfanilamide and related substances⁴⁷. The substances were introduced by Domagk in 1935 and tested clinically by French investigators and by Colebrook and his co-workers⁴⁸. The papers of Colebrook⁴⁹ indicate the bene-

46 Brightman, I. J., and Trask, J. D. Recovery of a Filtrable Virus from Children with Influenza. I. Epidemiologic and Clinical Observations, *Am J Dis Child* **52** 67-77 (July) 1936. Brightman, I. J. Recovery of Filtrable Virus from Children with Influenza. Experimental Disease in Ferrets, *ibid* **52** 78-91 (July) 1936.

47 Sulfanilamide and Related Compounds, report of the Council on Pharmacy and Chemistry *J A M A* **108** 1888-1890 (May 29) 1937.

48 Domagk, G. Ein Beitrag zur Chemotherapie der bakteriellen Infektionen, *Deutsche med Wchnschr* **61** 250-253 (Feb 15) 1935. Trefouel J., Trefouel, J., Nitti, F., and Bovet, D. Activite du p-aminophenylsulfamide sur les infections streptococciques experimentales de la souris et du lapin, *Compt rend Soc de biol* **120** 756-758, 1935. Buttle, G. A. H., Gray, W. H., and Stephenson, D. Protection of Mice Against Streptococcal and Other Infections by p-Aminobenzenesulphonamide and Related Substances, *Lancet* **1** 1286-1290 (June 6) 1936.

49 Colebrook, L., and Kenny, M. Treatment of Human Puerperal Infections, and of Experimental Infection in Mice, with Prontosil, *Lancet* **1** 1278-1286 (June 6) 1936. Treatment with Prontosil of Puerperal Infections Due to Haemolytic Streptococci, *ibid* **2** 1319-1322 (Dec 5) 1936. Colebrook, L., Buttle, G. A. H., and O'Meara, R. A. Q. The Mode of Action of p-Aminobenzenesulphonamide and Prontosil in Hemolytic Streptococcal Infections, *ibid* **2** 1323-1326 (Dec 5)

ficial effect of these substances in puerperal infections due to hemolytic streptococci. Striking results were obtained in 64 cases, in 12 of which bacteremia existed before treatment was started. The drug protected mice against experimental infection with this organism but had less effect against infection with meningococci and none against infection with pneumococci or staphylococci. Recovery has been reported in several cases of hemolytic streptococcic meningitis after chemotherapy.⁵⁰

References to other papers on the subject published in European journals are given in a paper by Long and Bliss,⁵¹ who confirmed many of the observations and add numerous data of their own. They found that the chemical exerted greater bacteriostatic action on certain strains of hemolytic streptococci than on others. The therapeutic effects were said to be remarkable. They report a series of 19 cases of infection with hemolytic streptococci in which favorable results were apparently due to the drug, but they cautiously add that the results noted may have been due to chance. Nevertheless, the careful clinical use of the compounds is warranted in the treatment of infections due to *Streptococcus haemolyticus*. In a later paper⁵² they report a series of 74 cases, with only 4 deaths. Marshall⁵³ has found that the absorption of the drug from the intestinal tract is nearly complete in four hours. The drug is excreted in the urine when an equilibrium between intake and output is established after two or three days of treatment. The drug appears also in the spinal fluid after oral administration. Fortunately, sulfanilamide has several desirable qualities. It is of low toxicity, it is easily administered and absorbed, it is not too expensive, it seems to be more effective in vivo than in vitro and it seems to be more effective against virulent strains than against avirulent ones. Untoward

1936 Foulis, M. A., and Barr, J. B. Prontosil Album in Puerperal Sepsis, *Brit. M. J.* **1** 445-446 (Feb. 27) 1937. Mellon, R. R., Gross, P., and Cooper, F. B. Experimental Studies with Sulfanilamide and with Prontosil, *J. A. M. A.* **108** 1858-1861 (May 29) 1937.

50 Anderson, E. D. Hemolytic *Streptococcus* Meningitis, *J. A. M. A.* **108** 1591-1592 (May 8) 1937. Weinberg, M. H., Mellon, R. R., and Shinn, L. E. Two Cases of Streptococcic Meningitis Treated Successfully with Sulfanilamide and Prontosil, *ibid.* **108** 1948-1951 (June 5) 1937. Schwentker, F. F., Clason, F. P., Morgan, W. A., Lindsay, J. W., and Long, P. H. The Use of Para-Amino-Benzene-Sulphonamide or Its Derivatives in the Treatment of Beta Hemolytic Streptococcal Meningitis, *Bull. Johns Hopkins Hosp.* **60** 297-306 (April) 1937.

51 Long, P. H., and Bliss, E. A. Para-Amino-Benzene-Sulfonamide and Its Derivatives, *J. A. M. A.* **108** 32-37 (Jan. 2) 1937.

52 Long, P. H., and Bliss, E. A. Para-Aminobenzenesulfonamide and Its Derivatives, *Arch. Surg.* **34** 351-359 (Feb.) 1937.

53 Marshall, R. K., Kendall, E., and Cutting, W. C. Para-Amino-Benzene-Sulfonamide (Prontylin), *J. A. M. A.* **108** 953-957 (March 20) 1937.

effects noted are the development of acidosis,⁵⁴ anemia,^{54a} jaundice, sulfhemoglobinemia and slight hematuria. Two deaths have been recorded, one⁵⁵ during administration of the drug and the other⁵⁶ as a result of sulfhemoglobinemia several days afterward. The presence of the benzene ring must be considered in regard to its possible effect on the granulocytes of the blood.

The mechanism of the effectiveness of sulfanilamide is unknown. Apparently hemolytic streptococci are not destroyed by the drug or by compounds formed from it. Bliss and Long⁵⁷ however, suggest that reduced prontosil⁵⁸ is bacteriostatic, indicating the probable importance of the process of reduction. The frequency of acidosis in patients treated with this drug suggests the possibility that this factor is important in the antibacterial effect of the drug *in vivo*. It is presumed that the capsule of the organism is injured, that toxin formation is inhibited or that the reticulo-endothelial system is specifically activated, none of which theories is as yet proved.

The drug apparently has been received with the usual amount of overenthusiasm attendant on the introduction of any new remedy. Even Domagk has expressed his surprise over its widespread use. In the next few years one may anticipate a flood of papers on the subject describing the effects of the drug in a great variety of infections, but at present it appears to be of value only for infections caused by hemolytic streptococci and only against certain strains of this organism and possibly against meningococci and gonococci. Reports have already appeared of its use in infections caused by typhoid bacilli, in undulant fever and in gas gangrene. One must be exceedingly wary of early favorable reports which, although apparently convincing, make one mindful of the failure and disappointments with ethylhydro-

54 Southworth, H. Acidosis Associated with Administration of Para-Amino-Benzene-Sulfonamide (Prontylin), *Proc Soc Exper Biol & Med* **36** 58-61 (Feb) 1937

54a Harvey, A. M., and Janeway, C. A. The Development of Acute Hemolytic Anemia During the Administration of Sulfanilamide, *J A M A* **109** 12-16 (July 3) 1937

55 Sommer, F. Ein Zwischenfall nach intravenösen Prontosil-Injektion, *Med Klin* **32** 1076-1077 (Aug 7) 1936

56 Frost, L. D. B. Sulphæmoglobinaemia Following Antistreptococcal Chemotherapy, *Lancet* **1** 510 (Feb 27) 1937

57 Bliss, E. A., and Long, P. The Activation of "Prontosil Solution" *In Vitro* by Reduction with Cystine Hydrochloride, *Bull Johns Hopkins Hosp* **60** 149-153 (Feb) 1937

58 The term prontosil has been used for a number of related substances. Bliss and Long used the disodium salt of 4'-sulphanildiphenyl-2-azo-7-acetylamino-1-hydroxynaphthalene-3,6-disulphonic acid.

cupreine, mercurochrome, acriflavine and other substances once so enthusiastically received. It is hoped that physicians will be critical in testing sulfanilamide and use it only for diseases against which controlled investigation has shown it to be of value, namely, infections caused by hemolytic streptococci.

Bacteriology—Tillett⁵⁹ observed that serum obtained from patients during acute infections of various types has a bactericidal effect on hemolytic streptococci. Serum of the same patients soon after recovery or marked improvement no longer had this effect. Different strains of streptococci differed somewhat in susceptibility to the bactericidal effects. He noted a close parallelism between the bactericidal activity of the serum and the temperature level of the patient when the serum was taken, but he could not ascertain whether the fever or certain unknown factors inherent in febrile disease were responsible for the effect. The agglutinins or other measurable factors were apparently not involved. The bactericidal effect of the serum was inactivated by heat, and no effect was obtained when the test was made under anaerobic conditions.

It is difficult to correlate these results in vitro with those sometimes noted clinically. For example, it has long been believed that certain infections, like influenza, render the body especially favorable for the growth of hemolytic streptococci. Occasionally the organisms invade the blood of patients ill with pneumococcic pneumonia,³⁴ but more often they become invasive some time after the crisis. Serum is bactericidal for other organisms as well.⁶⁰

In studying fibrinolysis, heretofore believed to be a property peculiar to the hemolytic streptococcus, Neter and Witebsky⁶¹ found that *Streptococcus viridans*, *Bacillus lactis-aerogenes*, Friedlander's bacillus and the pneumococcus were also able to produce fibrinolysis if grown in broth containing 2 per cent dextrose. The hemolytic streptococcus was the only one of the group tested which produced fibrinolysis in mediums of low sugar content. In another paper⁶² the authors report

59 Tillett, W. S. The Bactericidal Action of Human Serum on Hemolytic Streptococci. Observations Made with Serum from Patients with Acute Infections and from Normal Individuals, *J. Exper. Med.* **65** 147-162 (Jan.) 1937, Bactericidal Action of Human Serum on Hemolytic Streptococci. Factors Which Influence Phenomenon in Vitro, *ibid.* **65** 163-176 (Jan.) 1937.

60 Gordon, J., and Hoyle, L. The Bactericidal Action of Serum Against Meningococcus, Gonococcus and Micrococcus Catarrhalis, *J. Path. & Bact.* **43** 537-544 (Nov.) 1936.

61 Neter, E., and Witebsky, E. Fibrinolytic Activity of Hemolytic Streptococci and Other Microorganisms, *Proc. Soc. Exper. Biol. & Med.* **34** 549-552 (May) 1936.

62 Witebsky, E., and Neter, E. Properties of Different Fibrinolysins Produced by Streptococci, *Proc. Soc. Exper. Biol. & Med.* **34** 858-863 (June) 1936.

the production of an anticoagulant by hemolytic streptococci grown in 2 per cent dextrose broth Dart⁶³ confirmed their observation but is unable to attach any clinical significance as yet to the development of the anticoagulant

In discussing the clinical significance of fibrinolysis Waaler⁶⁴ states that although the highest resistance to it is found in the blood after infections with hemolytic streptococci, resistance may occur also after pneumococcic pneumonia In regard to rheumatic fever and rheumatoid arthritis, he doubts whether the antifibrinolytic quality of the serum justifies the assumption of a significant association between hemolytic streptococci and chronic arthritis

Clinical Investigations—Important epidemiological studies were made by English investigators⁶⁵ which demonstrated the value of accurate classification of bacteria In one hospital during a period of three and one-half years, fourteen outbreaks of infections due to hemolytic streptococci were traced The outbreaks usually occurred in the winter and were followed from patient to patient by the method for serologic classification devised by Griffith Only by this method could the extent of spread of a specific bacterium be appreciated When a certain type of streptococcic infection flared up, the infections in various persons were all due to the same type The organisms were apparently disseminated by droplet infection and transmitted from patient to patient or through the agency of carriers to other patients The clinical manifestations in different patients infected with the same type of organism varied greatly In some there developed pharyngitis, otitis media or mastoiditis, in others, adenitis, erysipelas, scarlet fever, bronchopneumonia or septicemia Operations on the nose and throat seemed to render patients more susceptible In regard to the latter point, van der Hoeden⁶⁶ also points out the importance of local trauma in predisposing to infection He cites several cases of subacute bacterial endocarditis occurring after dental extraction, paratyphoid fever after cholecystectomy, infection with *Bacillus proteus* after operation and fever following catheterization

63 Dart, E E Streptococcus Anticoagulant, Proc Soc Exper Biol & Med **35** 285-286 (Nov) 1936

64 Waaler, E Development of Antifibrinolytic Properties in Blood of Patients with Rheumatic Fever, Chronic Infective Arthritis and Bacterial Endocarditis, J Clin Investigation **16** 145-153 (Jan) 1937

65 Okell, C C, and Elliott, S D Cross-Infection with Hemolytic Streptococci in Otorhinological Wards, Lancet **2** 836-842 (Oct 10) 1936 Brown, W A, and Allison, V D Infection of Air of Scarlet-Fever Wards with Streptococcus Pyogenes, J Hyg **37** 1-14 (Jan) 1937

66 van der Hoeden, J Bacteremia and Bacterial Localization, Nederl tijdschr v geneesk **81** 337-340 (Jan 23) 1937

Gottlieb⁶⁷ studied 30 cases of recurrence of scarlet fever which occurred between the twentieth and the thirtieth day after the first attack. The most likely explanation of the recurrence, he believes, is reinfection with a different type of streptococcus. His impression was supported by finding different types of streptococci in different patients with scarlet fever. Brody and Smith⁶⁸ made a careful pathologic study of scarlet fever and reviewed the literature on the subject. They found the pathologic changes in scarlet fever to be of a single type. The lesions were located primarily in blood vessels, with secondary infiltration into the adjacent interstitial tissues. Streptococci were rarely present in the lesions, which seemed to be due more to the action of circulating toxin. Hemolytic streptococci were, however, recovered in the majority of cases in postmortem cultures of blood and from visceral organs.

Pollock⁶⁹ analyzed 42 cases of streptococcic peritonitis. The infection was usually preceded by pharyngitis and became manifest with early abdominal distention, pain and tenderness. Definite diagnosis was made by abdominal puncture. The mortality rate was 80 per cent. Treatment is unsatisfactory. A case of endocarditis⁷⁰ and 2 cases of meningitis caused by enterococci are reported.⁷¹

A rather surprising paper⁷² has been published dealing with the treatment of subacute bacterial endocarditis by splenectomy. The authors describe 4 cases, in 2 of which the diagnosis was doubtful. Splenectomy was performed, and all 4 patients died, 3 within three months and 1 in nine months, yet the authors believe that "life was unquestionably prolonged" by the operation. No necropsy report is given. They support their idea that splenectomy may be of value in sepsis with the doubtful hypothesis that the manufacture of toxins in secondary foci, such as the spleen, may be a chief cause of death. No one has as yet demonstrated a toxin in the infection in question.

67 Gottlieb, E. So-Called Recurrence of Scarlet Fever, *Ugeskr f læger* **98** 1054-1058 (Oct 29) 1936

68 Brody, H, and Smith, L. W. The Visceral Pathology in Scarlet Fever and Related Streptococcus Infections, *Am J Path* **12** 373-392 (May) 1936

69 Pollock, L. H. Primary Streptococcic Peritonitis, *Arch Surg* **33** 714-732 (Oct) 1936

70 Waaler, E. Bacterial Endocarditis Caused by Hemolytic Fecal Streptococci (Enterococci), *Acta med Scandnav* **91** 121-159 (Jan 20) 1937

71 Lang, F. J., Lode, A., and Schmuttermayer, F. Ueber Enterokokken-Infektionen im Zentralnervensystem, *Wien klin Wchnschr* **50** 29-35 (Jan 8) 1937

72 Riesman, D., Kolmer, J. A., and Polowe, D. Splenectomy in the Treatment of Subacute Bacterial Endocarditis *Am J M Sc* **192** 475-483 (Oct) 1936

Furthermore, one is tempted to inquire about the importance of other secondary foci or of the primary focus itself, as discussed last year by Hamman and Rienhoff⁷³. It seems that there is but little, if anything, to support the suggestion of splenectomy for septicemia due to any organism.

Muether and Kinsella⁷⁴ succeeded in producing endocarditis and septicemia in dogs. They first injured the valves of the heart surgically and then fed the animals a culture of *Str. viridans* obtained from a patient with subacute bacterial endocarditis. Five of the 12 dogs studied died. Necropsy showed bacterial endocarditis with vegetations.

Coburn and Moore⁷⁵ studied the relationship between *Str. haemolyticus* and erythema nodosum. By intracutaneous injection of the nucleoprotein derived from hemolytic streptococci they caused a local inflammatory reaction in 12 patients with erythema nodosum. In 6 patients recrudescences developed in previously affected areas shortly after the inflammatory reaction was noted. Spink⁷⁶ also studied the problem. In his opinion the lesions of erythema nodosum resembled histologically those produced by the injection of streptococci and broth filtrates of these organisms. A similar lesion was produced by the injection of tuberculin. He believes that erythema nodosum is a non-specific inflammatory reaction of the skin to a variety of bacterial, toxic and chemical agents.

Dental Infection—A valuable contribution to the bacteriology of the apexes of the teeth was made by the Dental Study Unit at Yale Medical School and is reported by Burket⁷⁷. After a thorough review of the literature, in which great diversity of findings and opinions was noted, they made a careful study of the correlation of the bacteriologic, roentgenographic, gross anatomic and necropsy observations made on the teeth of patients. The meticulous care used in making the study enhances the value of the work. They found, as have others before, that organisms could be isolated from about 50 per cent of

73 Hamman, L., and Rienhoff, W. F., cited by Reimann, H. A. Infectious Diseases. Review of the Current Literature, *Arch Int Med* **58** 329-370 (Aug) 1936.

74 Muether, R. O., and Kinsella, R. A. Bacterial Endocarditis Following the Ingestion of Bacteria, *J Clin Investigation* **15** 449 (July) 1936.

75 Coburn, A. F., and Moore, L. V. Experimental Induction of Erythema Nodosum, *J Clin Investigation* **15** 509-511 (Sept) 1936.

76 Spink, W. W. Pathogenesis of Erythema Nodosum, with Special Reference to Tuberculosis, Streptococcal Infection and Rheumatic Fever, *Arch Int Med* **59** 65-82 (Jan) 1937.

77 Burket, L. W. Studies of the Apexes of Teeth, *Yale J Biol & Med* **9** 271-286 (Jan), 348-358 (March) 1937.

the 419 periapical areas cultured Streptococci, especially those of the viridans type, were present in 89 per cent of teeth, with positive results of culture. Staphylococci were next in order of frequency. Growth was obtained from 30 per cent of teeth without roentgenographic evidence of rarefaction at the root, from 76 per cent of those with a small periapical area lucent to roentgen rays and from 60 per cent of those with a large lucent area. Classified according to gross anatomic changes, organisms were isolated from 43 per cent of clinically normal teeth, from 38 per cent of carious teeth and from 72 per cent of "dead" teeth. The highest percentage of pure cultures was obtained from teeth with no periapical roentgenographic changes.

This report should be carefully studied by those who still attach undue importance to teeth as foci of infection, especially to roots which are so often erroneously regarded as "abscessed" simply because of apical lucency. It is obviously impossible to learn whether or not a root is "infected" by means of roentgen shadows alone. All rarefied areas are certainly not abscesses or the result of abscesses. It is urgently desired that this study group continue their investigation to determine the pathologic significance of teeth regarded as "infected" on such weak evidence.

RHEUMATIC FEVER

Several studies have dealt with the unsettled problem of the relation of hemolytic streptococci to rheumatic fever. Two English observers⁷⁸ emphasized the constitutional factors especially pertaining to abnormal capillary circulation. Persons of this type when exposed to cold and damp are more apt to have arthritis than normal persons. Infection, they believe, is the most important factor in predisposing patients to arthritis, and the hemolytic streptococcus is the most frequently incriminated organism. Keefer and Spink,⁷⁹ however, point out the contradictory fact that rheumatic fever was not noted to follow in any of 1,400 cases of erysipelas which they reviewed. Other studies, they claim, also fail to mention erysipelas as a prelude to rheumatic fever, whereas certain infections with hemolytic streptococci commonly precede it. They found the strains of streptococci isolated from patients with erysipelas to be no different from those causing other types of infection. Edstrom⁸⁰ observed several cases of rheumatic fever which followed trauma to a single joint, further adding to the obser-

78 Goldie, W, and Griffiths, G. J. Aetiological Relation of the Streptococcus Haemolyticus to the "Rheumatic" Diseases, *Brit. M. J.* **2** 755-757 (Oct. 17) 1936.

79 Keefer, C. S., and Spink, W. W. Studies of Hemolytic Streptococcal Infection, *J. Clin. Investigation* **16** 155-159 (Jan.) 1937.

80 Edstrom, G. Mechanisches Trauma und nachfolgende Febris rheumatica, *Acta med. Scandinav.* **88** 342-353, 1936.

vations of Bland and Jones mentioned in last year's review⁸¹ Swift informs me that sulfanilamide had no beneficial effect on acute rheumatic fever

Rinehart and his associates⁸² found the vitamin C content of the blood in cases of rheumatic fever and rheumatoid arthritis to be uniformly reduced The low levels may be raised by giving vitamin C They could not ascertain whether the low level was due to inadequate intake, anorexia, digestive disorder or the disease itself

Coburn and Moore⁸³ advance further evidence to illustrate the independence of chorea and rheumatic fever They agree with other authors mentioned in the review⁸¹ last year that the physiologic background prerequisite to the development of chorea may be prepared by a variety of abnormal conditions, of which the rheumatic state may be one They found that in three fourths of the cases of chorea studied the condition was independent of rheumatic fever Bourne⁸⁴ describes a case in which he regards chorea as due to acute rheumatic meningitis Signs of meningitis developed during an attack of rheumatic fever The spinal fluid was sterile and contained 78 leukocytes per cubic millimeter

Wolffe and Brim⁸⁵ describe cases of rheumatic fever in children characterized by recurrent abdominal cramps The problem of rheumatic involvement of the appendix is considered by others⁸⁶

Massel, Mote and Jones⁸⁷ injected 2 or 3 cc of serum from patients with rheumatic fever subcutaneously into the patients' own tissue A control group of normal persons and patients with chorea were similarly studied Typical subcutaneous nodules developed in

81 Reimann, H A Infectious Diseases Review of the Current Literature, *Arch Int Med* **58** 329-370 (Aug) 1936

82 Rinehart, J F, Greenberg, L D, and Baker, F Reduced Ascorbic Acid Content of Blood Plasma in Rheumatoid Arthritis, *Proc Soc Exper Biol & Med* **35** 347-350 (Nov) 1936 Rinehart, J F, Greenberg, L D, and Christie, A V Reduced Ascorbic Acid Content of Blood Plasma in Rheumatic Fever, *ibid* **35** 350-353 (Nov) 1936

83 Coburn, A F, and Moore, L V The Independence of Chorea and Rheumatic Activity, *Am J M Sc* **193** 1-4 (Jan) 1937

84 Bourne, G Acute Rheumatic Meningitis, *Brit M J* **2** 1017-1018 (Nov 21) 1936

85 Wolffe, J B, and Brim, C J Abdominal Syndrome of Rheumatic Disease in Childhood, *Am J Dis Child* **52** 296-303 (Aug) 1936

86 Martin, A T, and Ellenberg, S L Rheumatic Involvement of the Appendix, *J Pediat* **9** 234-239 (Aug) 1936

87 Massel, B F, Mote, J R, and Jones, T D The Artificial Induction of Subcutaneous Nodules in Patients with Rheumatic Fever, *J Clin Investigation* **16** 125-128 (Jan) 1937

90 per cent of the patients with rheumatic fever who had received injections of their own serum, in 14 per cent of those with clinical evidences of infection, in 14 per cent of patients with chorea and in 3 per cent of normal persons

The subject of chronic arthritis and rheumatism is reviewed in a comprehensive manner elsewhere⁸⁸ and need not be dealt with here

STAPHYLOCOCCIC INFECTIONS

Numerous studies have been made of the treatment of infections caused by staphylococci. Clinical reports⁸⁹ on osteomyelitis stress the importance of the toxins elaborated by the organisms and of the use of immune serum in treatment. Since staphylococcus toxoid raises the titer of immune bodies in man, staphylococcus antitoxin may be of value in treatment. Immunotransfusion from a person convalescent from staphylococcic infection whose blood contains antitoxin is said to be of value. Another report⁹⁰ also emphasizes the toxemic symptoms of osteomyelitis. The authors state that commercial antitoxins neutralize in vivo the toxins of heterologous strains of staphylococci. They treated 16 patients with prompt drainage and multiple blood transfusions, 8 of whom recovered, in contrast with 11 recoveries among 13 patients treated with staphylococcus antitoxin. Buchman,⁹¹ on the other hand, is not enthusiastic about the effects of toxoid in osteomyelitis. Among his patients who had been treated the magnitude of the titer of immune bodies gave no indication as to the progress of the disease for better or for worse. He attributes the disappointing results observed to the possibility that in the type of infection dealt with antitoxic immunity was not as important as the establishment of resistance to invasiveness, which toxoid does not provide. Dolman's favorable conclusions, Buchman claims, deal with generalities and impressions without adequate control and are insufficient to warrant enthusiasm. A good bibliography of the subject accompanies this paper. It is obvious that knowledge of staphylococcic infection is as yet too meager to permit one to speak with any certainty of specific treatment.

88 Hensch, P. S., Bauer, W., Fletcher, A. A., Ghrist, D., Hall, F., and White, T. P. The Problem of Rheumatism and Arthritis. Review of American and English Literature for 1935, *Ann Int Med* **10** 754-909 (Dec.) 1936. This is a review of 530 papers.

89 Stookey, P. F., Scarpellino, L. A., and Weaver, J. B. Immunology of Osteomyelitis, *Arch Surg* **32** 494-505 (March) 1936.

90 Joyner, A. L., and Smith, D. T. Acute Staphylococcus Osteomyelitis, *Surg, Gynec & Obst* **63** 1-6 (July) 1936.

91 Buchman, J. The Use of Staphylococcus Toxoid in the Treatment of Chronic Osteomyelitis, *J A M A* **108** 1151-1156 (April 3) 1937.

Fisher⁹² demonstrated plasma coagulation and fibrinolytic properties of staphylococci. Twenty-six of the thirty-four strains tested clotted plasma. All of the thirty strains from human sources clotted plasma. The inactive strains were usually of the albus nonhemolytic type, which are usually saprophytic. A strain which does not clot plasma almost certainly lacks pathogenicity. Fisher was unable to cause intravascular clotting. In further studies fifteen of twenty-six strains were slowly fibrinolytic. The author suggests that the spread of staphylococcal infection in patients may be related to the ability of the organisms to dissolve clots.

Julianelle⁹³ introduces a simpler method for the differentiation of staphylococci. He found that most pathogenic, type A, strains ferment mannitol, while most nonpathogenic, type B, strains do not. The error of the method was within 5 per cent.

MENINGITIS

A number of papers dealing with meningococcal infection have been published. Branham,⁹⁴ in discussing the significance of types states that certain changes are necessary in the classification of meningococci. Type I and type III meningococci, for example, have become so closely interrelated that for practical purposes differentiation no longer seems to be necessary. The type I to type III group has apparently become predominant in many parts of the world. Type II and type IV are entirely distinct from types I to III and from each other, so that it seems necessary to deal with three general types, namely, I to III, II and IV. Type II meningococci are found largely in carriers and seldom in persons with disease, except in the cases of relatively mild or chronic septicemia. On the other hand, meningococcal endocarditis in nearly all cases has been due to organisms of the type I to type III group.

There is still difference of opinion as to whether or not type specific serum is effective only for the homologous type of organism. As Branham further points out, confusion has arisen in regard to the classification of meningococci according to type on an immunologic basis. During twenty years of observation certain strains have definitely changed their antigenic pattern. For example, a certain known strain of type I organism has apparently changed so that it now conforms

92 Fisher, A. M. The Plasma-Coagulating Properties of Staphylococcus, *Bull. Johns Hopkins Hosp.* **59** 393-414 (Dec.) 1936, The Fibrinolytic Properties of Staphylococci, *ibid.* **59** 415-426 (Dec.) 1936.

93 Julianelle, L. A. Determination of Staphylococcal Types by Fermentation of Mannite, *Proc. Soc. Exper. Biol. & Med.* **36** 117-119 (March) 1937.

94 Branham, S. E. The Significance of Serologic Types Among Meningococci, *J. A. M. A.* **108** 692-696 (Feb. 27) 1937.

with the characteristics of type III. In considering epidemiological problems it is important that a world-wide type standard be established.

Alexander⁹⁵ tested the prognostic value of the precipitin ring test. Of 22 patients for whom the test gave positive results in ten minutes, 77 per cent died, in contrast with 4 per cent of the 47 patients for whom the test gave negative results. Brianham states that the ring test can be performed at the bedside to determine the type of meningococcus and the selection of the proper type-specific therapeutic serum.

Hoyne⁹⁶ emphasizes the importance of regarding meningeal involvement as part of a systemic infection, the point being that intravenous serum therapy is of more value than intraspinal treatment. He treated all of his 66 patients intravenously, 31 received the new antitoxic serum and 35 the usual antimeningococcus serum. For those receiving antitoxic serum the fatality rate was 6.4 per cent, and the number of days spent in the hospital averaged 14.5, for those receiving antiserum the death rate was 14.2 per cent, and the number of days spent in the hospital averaged 15.3. Typing of meningococci was not considered. The death rate for the whole series of patients receiving intravenous therapy alone was 11.8 per cent, as compared with 50 per cent for the patients observed prior to 1934.

In discussing Hoyne's paper Kempf states that in a small series of his own patients the relative merits of antitoxin versus antimeningococcus serum reversed. Certain investigators in this field are unconvinced that the meningococcus actually produces a toxin.

Proom⁹⁷ found that sulfanilamide protected mice from meningococcic infection, but only if given immediately after the infection had developed. Schwentker, Gelman and Long⁹⁸ used sulfanilamide in the treatment of 10 patients with meningococcic meningitis. The results are said to be favorable and comparable to those which follow treatment with antiserum. Too few patients were treated to permit the drawing of definite conclusions regarding its use.

Reports of 2 cases of meningococcic myocarditis and a discussion of chronic meningococcic septicemia have been published⁹⁹. Because

95 Alexander, H. E. Prognostic Value of Precipitin Test in Meningococcus Meningitis, *J Clin Investigation* **16** 207-213 (March) 1937.

96 Hoyne, A. L. Intravenous Treatment of Meningococcic Meningitis with Meningococcus Antitoxin, *J A M A* **107** 478-481 (Aug. 15) 1936.

97 Proom, H. The Therapeutic Action of *p*-Aminobenzenesulphonamide in Meningococcal Infection of Mice, *Lancet* **1** 16-18 (Jan. 2) 1937.

98 Schwentker, F. F., Gelman, S., and Long, P. H. The Treatment of Meningococcus Meningitis with Sulfanilamide, *J A M A* **108** 1407-1408 (April 24) 1937.

99 Saphir, O. Meningococcic Myocarditis, *Am J Path* **12** 677-689 (Sept.) 1936. Appelbaum, E. Chronic Meningococcus Septicemia, *Am J M Sc* **193** 96-108 (Jan.) 1937.

of certain biologic similarities of heat liability between meningococci and gonococci and the favorable effects reported by treating gonococcic infections with heat, it was obvious that the same treatment should be tested for meningococcic infections. In experiments thus far reported¹⁰⁰ most strains of meningococci were killed after eight hours at 41.5 C (106.8 F). On the basis of these findings 2 patients with chronic meningococcic infections were treated, and cure was said to have resulted from fever therapy. The authors do not recommend the use of fever therapy in acute meningococcic meningitis. Platou, McElmeel and Stoesser,¹⁰¹ however, report the use of three sessions of fever therapy on alternate days for a child of 3½ years with acute meningococcic septicemia. Recovery followed.

Acute Lymphocytic Meningitis—This type of meningitis is now established as a specific infectious disease caused by a filtrable virus. Viets and Warren¹⁰² review the literature on the subject since 1934 and add several cases of their own, with careful histopathologic studies of a fatal case. Their cases illustrate three types of the disease—transient, prolonged and fatal. The clinical picture is similar in all three, differing only as to degree of severity. An epidemic involving 22 children in Cincinnati in the summer of 1935 is reported by Dummer and his associates.¹⁰³ The clinical characteristics were headache, vomiting and abdominal pain. Rigidity of the neck and the Kernig and the Brudzinski sign were frequently present. The cell count of the spinal fluid was usually elevated to 200 cells per cubic millimeter. Lymphocytes predominated, and the globulin content was increased in about half the patients. The fever lasted only a few days, and recovery was rapid and complete, with no sequela. There was no evidence of contagion, since the patients lived in widely separated areas. Charleux^{103a} suggests that the disease may be acquired from dairy products.

100 Bennett, A. E., Person, J. P., and Simmons, E. E. Treatment of Chronic Meningococcic Infections by Artificial Fever, *Arch. Phys. Therapy* **17** 743-749 (Dec.) 1936.

101 Platou, E. S., McElmeel, E., and Stoesser, A. V. Artificial Fever in the Treatment of Meningococcus Infection, *Minnesota Med.* **19** 781-782 (Dec.) 1936.

102 Viets, H. R., and Warren, S. Acute Lymphocytic Meningitis, *J. A. M. A.* **108** 357-361 (Jan. 30) 1937.

103 Dummer, C. M., Lyon, R. A., and Stevenson, F. E. Benign Lymphocytic Meningitis (Aseptic Meningitis), *J. A. M. A.* **108** 633-636 (Feb. 20) 1937.

103a Charleux, G. La meningite benigne des porchers, *Presse med.* **45** 452-454 (March 24) 1937.

ENCEPHALITIS

Burdon, Thurston, Varney and Bronfenbrenner¹⁰⁴ followed Rosenow's technic carefully in studying the etiologic significance of streptococci in epidemic encephalitis. While the majority of cultures of material from the brain showed no growth and rarely streptococci, in agreement with the observations of others, culture of material from the nasopharynx showed a predominance of green-producing streptococci. No significant results were obtained with agglutination tests, however, nor could the authors confirm Rosenow's measurements of cataphoretic velocity. In a second study they could establish no biologic relationship between streptococci and the virus isolated from patients with the disease in St. Louis. No evidence was found to support the view that streptococci represent the primary etiologic agents of epidemic encephalitis. In spite of a great mass of evidence to the contrary,¹⁰⁵ Rosenow¹⁰⁶ seems oblivious to all criticism and continues to champion his views undaunted. He now has a "virus derived from streptococci" which produces first encephalitic and then poliomyelitic lesions in monkeys.

An epidemic of encephalitis involving 160 persons occurred in Pennsylvania in the summer of 1935.¹⁰⁷ It began in July and lasted until September. The infection appeared to be spread by droplet infection, for it was contagious and affected entire families in some cases. Children and young adults were chiefly involved. The incubation period varied from three to ten days. Headache, nausea, vomiting, photophobia, stiffness of the neck, backache, cramps, muscle pains, nervousness, insomnia and vertigo were common complaints. Physical signs were minimal. The Kernig sign was noted occasionally. Sore throat was almost always present. The cell count and the globulin content of the spinal fluid were increased even in cases of subclinical encephalitis. The disease was mild, as a rule, and few sequelae followed. Only 1 patient died. The use of convalescent serum seemed to be of value prophylactically and therapeutically.

104 Burdon, K. L., Thurston, E. W., Varney, P. L., and Bronfenbrenner, J. Etiologic Significance of Streptococci in Epidemic Encephalitis. Incidence of Streptococci in Cultures from Patients with Encephalitis in St. Louis and from Normal Controls, and Characteristics of Various Strains Isolated, *Arch. Int. Med.* **58**: 285-308 (Aug.) 1936, Etiologic Significance of Streptococci in Epidemic Encephalitis. Experiments with Animals and Conclusions, *ibid.* **58**: 469-494 (Sept.) 1936.

105 Rivers, T. M. Viruses and Koch's Postulates, *J. Bact.* **33**: 5-6 (Jan.) 1937.

106 Rosenow, E. C. Further Studies on the Relationship of Streptococci to the Viruses of Encephalitis and Poliomyelitis, *ibid.* **33**: 61-62 (Jan.) 1937.

107 Slesinger, H. A. Acute Epidemic Encephalitis, *Am. J. M. Sc.* **192**: 225-234 (Aug.) 1936.

POLIOMYELITIS

Nearly 11 000 cases of poliomyelitis were reported by the United States Public Health Service in 1935. An excellent survey of the problem of immunity in poliomyelitis has been published by Harmon and Harkins¹⁰⁸ who critically review recent studies on the subject and point out certain peculiarities of the disease which have been baffling. For example, a specific virus-neutralizing substance is found more often in adults without a history of contact or infection than in persons convalescing from the disease. The importance of attempts to increase immune substances artificially is therefore questioned. Because of the present uncertainty of methods in current use, the authors still recommend the employment of convalescent serum and other specific serum therapy since no evidence, they claim, has shown that they are not of value. Schultz,¹⁰⁹ however, in a paper presented before the International Congress for Microbiology in London, states that enough is now known about the pathogenic and immunologic features of the disease to cast considerable doubt on the belief that it will ever be controlled by means of serums or vaccines.

Howitt¹¹⁰ studied an outbreak of poliomyelitis in California and isolated a strain of virus which differed immunologically from other well known strains. She suggests the probability that various types of virus exist and produce diseases of clinically similar characteristics, which have come to be recognized as poliomyelitis.

Observation¹¹¹ was made of the effect of a preceding mild infection in producing resistance to poliomyelitis. Monkeys previously inoculated with the virus of dog distemper were inoculated with a strain of poliomyelitis which ordinarily killed them. The results were surprising in that 66 per cent of the inoculated animals recovered. It is assumed that the effects of the preceding distemper in some way protected the monkeys against poliomyelitis. Opportunity was provided to test the value of trinitrophenol and alum nasal spray in preventing poliomyelitis during an epidemic in Alabama.¹¹² The disease developed

108 Harmon P H and Harkins, H N. The Significance of Neutralizing Substances in Resistance and Recovery from Poliomyelitis, *J A M A* **107** 554-558 (Aug 22) 1936

109 Schultz E W. Immunity and Prophylaxis in Poliomyelitis, *J A M A* **107** 2102-2104 (Dec 26) 1936

110 Howitt, B F. A Recently Isolated Strain of Poliomyelitis Virus, *Science* **85** 268-270 (March 12) 1937

111 Dalldorf G, Douglass M, and Robinson H E. The Sparring Effect of Dog Distemper on Experimental Poliomyelitis, *Science* **85** 184-185 (Feb 12) 1937

112 Armstrong C. Experiences with Picric Acid-Alum Spray in Prevention of Poliomyelitis in Alabama 1936, *Am J Pub Health* **27** 103-112 (Feb) 1937

in a number of persons who had used the substance. The failure to protect suggested that the chemicals are not as effective and trustworthy in man as in animals.

Lucchesi¹¹³ believes that many patients in the Philadelphia area who showed fever, headache, cervical rigidity, vomiting and lymphocytes in the spinal fluid without paralysis actually were suffering from poliomyelitis. Because of the absence of paralysis the disease was probably erroneously diagnosed as choriomeningitis or encephalitis. It is obvious that great care must be taken in differentiating infections of this nature from one another. Biologic methods of diagnosis, though intricate, must be used more frequently, since clinical data alone are insufficient.

TULAREMIA AND PLAGUE

Tularemia—Foshay¹¹⁴ reports further observations on the cutaneous reaction which occurs after the intradermal injection of specific antiserum into patients suffering from tularemia. All of the 450 patients showed a positive reaction, while normal persons showed no response. The reaction is erythematous-edematous in nature and becomes maximal in from fifteen to twenty minutes. The reaction was diagnostically positive for tularemia in some cases on the first day of illness and in 1 case twenty-two years after recovery. The degree of perfection claimed for this test is remarkable and sets it apart from most other biologic tests, which are much more frequently unreliable. Foshay believes that the reaction is due to the antigen-antibody union, which involves only the species-specific polysaccharide. The suggestion is made that a similar test might be of value in diagnosis and treatment by determining the specificity of other infections as well.

In another study the same author¹¹⁵ found viable bacilli in certain patients long after there had apparently been full recovery from the initial infection. The observation illustrates the dictum that is true of many other infections, to wit, "once infected, always infected." The constant presence of organisms is a continuous source of danger, and exacerbations of disease flare up periodically when the delicate equilibrium between host and parasite is disturbed by various causes. The condition is exemplified in a patient who had intermittent symptoms and recurrent adenopathy for eight years. The persistence of *Pasteurella tularensis* in the body may explain the well known fact that agglutinins

113 Lucchesi, P. F. Nonparalytic Poliomyelitis Versus Choriomeningitis, J. A. M. A. **108** 1494-1496 (May 1) 1937.

114 Foshay, L. The Nature of the Bacterial-Specific Intradermal Antiserum Reaction, J. Infect. Dis. **59** 330-339 (Nov.-Dec.) 1936.

115 Foshay, L., and Mayer, O. B. Viability of *Bacterium Tularensis* in Human Tissues, J. A. M. A. **106** 2141-2143 (June 20) 1936.

for this organism persist for many years Blackford and Smith ¹¹⁶ also report a case in which bacilli were still obtainable from a lesion twenty-one months after the primary infection McGovern ¹¹⁷ describes a case in which the primary ulcer of tularemia appeared in the pharynx The patient crushed infected ticks and probably introduced the infection into his mouth with his fingers

A new and unexpected mode of transfer of tularemia is propounded by two Russian investigators ¹¹⁸ An epidemic broke out among some field workers, especially those who drank water from a brook which was inhabited by water rats Most of the patients had the "anginal" form of tularemia, while the rest showed the typhoid or oculoglandular form, which suggested that the infection was water borne and entered through the tonsils, the oral mucosa and the conjunctivae All guinea-pigs inoculated with the water under suspicion died of tularemia It is of interest to recall that a previous epidemic of tularemia in Russia was associated with rodents during a flood

In Austria ¹¹⁹ and Czechoslovakia ^{119a} tularemia has been recognized for the first time and has again been regarded by some as a new disease Among the 200 cases studied during the past year there were several of the newly recognized "anginal" form, with acute tonsillitis and swelling of the cervical lymph nodes It seems strange that a disease with symptoms and signs as characteristic as those of tularemia should have been overlooked in a country as medically advanced as Austria, yet I agree with Pilot that the disease doubtlessly existed unrecognized for many years

An epidemic of tularemia in Utah is reported on by Hillman and Morgan ¹²⁰ It involved 26 of a group of 170 men engaged in road work in hot weather Many of the men worked without shirts or other covering above the waist and were bitten by horse-flies or deer-flies In no instance did the disease develop in a fully clothed man The incident again calls forcibly to mind the chain of events or factors necessary in epidemics, namely, the source of infection (sick rabbits were noted in the vicinity), the great agent of conveyance (probably

¹¹⁶ Blackford, S D, and Smith, D C Prolonged Virulence of Bacterium Tularensis in Human Tissue, *South M J* **29** 1062-1067 (Nov) 1936

¹¹⁷ McGovern, F H Primary Tularemic Ulcers in the Pharynx, *J A M A* **107** 1629-1630 (Nov 14) 1936

¹¹⁸ Karpoff, S P, and Antonoff, M I Spread of Tularemia Through Water, as a New Factor in Its Epidemiology, *J Bact* **32** 243-259 (Sept) 1936

¹¹⁹ Tularemia in Austria *Foreign Letters, J A M A* **108** 1813-1814 (May 22) 1937

^{119a} Tomanek, E Tularemia in Czechoslovakia and Austria During 1936 and 1937, *Am J Pub Health* **27** 443 (May) 1937

¹²⁰ Hillman, C C, and Morgan, M T Tularemia, *J A M A* **108** 538-540 (Feb 13) 1937

deer-flies) and the susceptible host. It also emphasizes the importance of prophylaxis in avoiding insect bites in areas where tularemia is endemic.

It is now a well known fact that tularemia often breaks out as an epizootic when certain animal populations are high. Sylvest¹²¹ believes that tularemia may have been accountable for the great mortality rate among lemmings during their strange periodic migrations to the sea. Simultaneously an unusual disease in man was recognized for centuries in Norway. The descriptions of the disease, called lemming fever, as early as 1532 and 1633 coincided closely with that of tularemia.

Plague—Meyer¹²² discusses the controversy which has arisen over the relationship of "sylvatic" plague of wild rodents to the plague of the domestic rat, which is the usual source of the disease in human beings, although wild rodents apparently were responsible for the explosive outbreak in Manchuria in 1910 and in California in 1920. There is even uncertainty as to the choice of the term sylvatic or selvatic, the former seems to be preferable. There is reason to agree with Meyer that the variety of plague prevalent among rodents in the United States is different from that which caused the "black death." Type differentiation recognized for many other species of bacteria no doubt exists also among plague bacilli. According to recent reports of the United States Public Health Service, 2 cases of plague occurred in California, 1 case in Utah and 1 in Hawaii in 1936. Plague occurred in ground squirrels in California, Oregon, Montana and Idaho, in fleas from squirrels in Nevada and Washington, and in marmots and prairie dogs in Utah. Seventy-two species of rodents are known to suffer from plague. In this respect another similarity may be pointed out between the organism causing plague and its close relative *Past. tularensis*, which is also known to invade many species of animals and birds.

A comprehensive survey of plague has been published by Wu and his colleagues¹²³

UNDULANT FEVER

Hardy, Jordan and Borts¹²⁴ summarize the important advances in the knowledge of undulant fever. Undulant fever is really not one

121 Sylvest, E. Tularemia—Disease of Lemmings, *Ugeskr. f. læger* **98** 307-310 (April 9) 1936.

122 Meyer, K. F. The Sylvatic Plague Committee, *Am. J. Pub. Health* **26** 961-969 (Oct.) 1936.

123 Wu, L. T., Chun, J. W. H., Pollitzer, R., and Wu, C. Y. *Plague. A Manual for Medical and Public Health Workers*, Shanghai, Weishungshu National Quarantine Service, 1936.

124 Hardy, A. V., Jordan, C. F., and Borts, I. H. Undulant Fever, *J. A. M. A.* **107** 559-563 (Aug. 22) 1936.

disease but a group of three closely related diseases caused, respectively, by the bovine, the porcine and the caprine strain of *Brucella*. Disease due to the bovine variety is most prevalent in regions where this variety is most widely distributed, for example, in the eastern part of the United States. Disease due to the porcine variety occurs more often in the middle western states, where hogs are more common. *Brucella* of the porcine variety was recovered in 70 per cent of cases in Iowa and in 60 per cent in Minnesota¹²⁵. In the state of New York 93 per cent of isolated strains were of the bovine variety. The porcine variety is the more invasive and dangerous. It frequently gives rise to localized infections which are often suppurative, frequently involving the skeletal system. The recognition of these suppurative lesions as being caused by *Brucella* is one of the most important of recent contributions to clinical knowledge. Evans¹²⁶ reviews the history of undulant fever as derived from goats in the United States. The disease is believed to have existed in Texas for at least fifty years. Twelve cases were reported in 1911. Her own studies showed the prevalence of caprine strains in North Carolina and Kansas. Cattle were found to be frequently infected with the caprine variety, which is of significance, since infections caused by these organisms are usually severe.

The increasing number of cases reported (1,897 cases in 1935) is often believed to indicate a spread or an increase of undulant fever. It is far more likely, however, that it represents merely its more frequent recognition. Studies of the incidence of infection among cattle, as a matter of fact, show a surprisingly even distribution in all sections of the United States. It seems, then, that many more unrecognized or unreported cases exist among human beings. In regard to treatment, Hardy states that as yet no conclusive evidence as to the value of specific therapy has been obtained. A report¹²⁷ of the successful treatment of meningitis due to *Brucella* with immune serum from a convalescent patient has been published, but other workers¹²⁸ claim to have obtained good results, as have numerous observers previously in 10 of 12 patients with the nonspecific therapy consisting of injection of typhoid vaccine.

125 Kabler, P., and MacLanahan, M. A Differential Study of Forty *Brucella* Strains Isolated in Minnesota, *J. Infect. Dis.* **58** 293-298 (May-June) 1936.

126 Evans, A. C. The Distribution of *Brucella Melitensis* Variety *Melitensis* in the United States, *Pub. Health Rep.* **52** 295-303 (March 12) 1937.

127 Poston, M. A., and Smith, D. T. Successful Treatment of *Brucella* Meningitis with Immune Human Serum, *New England J. Med.* **215** 369-383 (Aug. 27) 1936.

128 Ervin, C. E., Hunt, H. F., and Niles, J. S. Foreign Protein Therapy, *Am. J. M. Sc.* **192** 234-241 (Aug.) 1936.

Prickman and Popp¹²⁹ treated 4 patients with the Simpson-Kettering hyperthermia with apparent good results, although they are cautious in drawing conclusions, realizing that undulant fever is a disease characterized by natural remissions and exacerbations. In another unusual case¹³⁰ of undulant fever with degenerative myositis, fever therapy was apparently of benefit.

Keller and his associates¹³¹ estimated the relative value of several diagnostic tests. The agglutination test was found to be most dependable for patients during the active stage of the disease but may often show negative results in those who have been infected previously. The intracutaneous test determines a state of allergy resulting from infection with *Brucella* and is useful in ascertaining the general incidence of infection in large groups of persons. The authors believe that the opsonocytophagic test gives the best information as to the status of immunity of the patient. It is possible, they state, to determine whether persons are susceptible, infected or immune by the use of the intracutaneous and the opsonocytophagic test together. From experience with complicated tests in other infections one wonders whether or not the last statement is not somewhat too optimistic. Actual immunity or susceptibility is often unrelated to measurable factors in the test tube.

Among the many manifestations of undulant fever, encephalitis was recently discussed¹³². In the author's 4 cases, however, the diagnosis of undulant fever must be accepted with reservation, since it was based on only a positive cutaneous reaction and positive results of agglutination tests. Furthermore, the possibility of the occurrence of "nonspecific" encephalitis, common to many other infections, must be considered.

TUBERCULOSIS

Only a few of the numerous papers on tuberculosis published in the past year are selected for comment here. Miller and Rappaport¹³³ in a timely paper point out the difficulties inherent in interpreting the reaction to injected tuberculin. Many factors, both specific and non-

129 Prickman, L. E., and Popp, W. C. Treatment of Brucellosis by Hyperpyrexia Induced by the Simpson-Kettering Hyperthermia, *Proc. Staff Meet., Mayo Clin.* **11** 506-510 (Aug. 5) 1936.

130 O'Donoghue, A. F., and Scott, W. Degenerative Myositis from Melitensis Infection, *Nebraska M. J.* **21** 462 (Dec.) 1936.

131 Keller, A. E., Pharris, C., and Gaub, W. H. Diagnosis of Undulant Fever, *J. A. M. A.* **107** 1369-1373 (Oct. 24) 1936.

132 McCullagh, E. P., and Clodfelter, H. M. Encephalitis Due to Undulant Fever. Report of Four Cases, *Ann. Int. Med.* **10** 1508-1513 (April) 1937.

133 Miller, J. A., and Rappaport, I. Resistance in Tuberculosis, *J. A. M. A.* **107** 471-474 (Aug. 15) 1936.

specific, condition the response. The specific factors concern acquired, inherited and accumulated resistance, while the nonspecific factor may be thought of as constitutional in nature. Since there exists no means of distinguishing these various factors and since the reaction to tuberculin consists of merely an allergic response, one therefore cannot know which of the factors are concerned. Conclusions based on the test alone may therefore be misleading.

Gardner¹³⁴ believes that the lesions of silicosis and those of tuberculosis are histologically similar. For instance, both conditions give rise to a primary mononuclear cell reaction and produce epithelioid and giant cells, both cause exudation and necrosis, and in each calcification may occur. The tuberculin test, however, elicits a positive reaction only in the presence of tuberculous disease. Gardner casts doubt on the specificity of certain chemical fractions of the tubercle bacillus in causing given cellular reactions, as shown by others.

Kereszturi and Park¹³⁵ report observations made over eight years on BCG vaccine. They believe it to be free from danger. The death rate from tuberculosis was twice as high among unvaccinated children. Among control patients who showed a negative reaction to the Mantoux test the death rate was four times as high as among infants vaccinated with BCG. They suggest that BCG be used as a public health measure for the prevention of tuberculosis in those who have not yet become infected and who may later be exposed. This study and the following one add support to the opinion of those who do not regard a positive reaction to the tuberculin test as a liability, as discussed in last year's review.⁸¹

Increased inflammation after reinfection, Lurie¹³⁶ thinks, may play a rôle in immunity. I believe with him that the allergic reaction, with its outpouring of exudate, may tend to fix organisms early and prevent their spread. Vaccination with BCG afforded pronounced protection. Contrary to previous general opinion, the humoral factor of immunity is thought to be important in tuberculosis. While the fibrin barriers erected at the site of the allergic reaction may localize small doses of bacilli, when large doses are used the increased lymphatic flow may bring about increased rapidity of dissemination. Much depends, it seems, on the intensity of the reaction, on the size of the dose of infect-

134 Gardner, L. U. Similarity of Lesions Produced by Silica and by Tubercle Bacillus, *Am J Path* **13** 13-25 (Jan) 1937.

135 Kereszturi, C., and Park, W. H. Use of BCG Vaccine Against Tuberculosis in Children. Eight Years' Experience, *Am Rev Tuberc* **34** 437-456 (Oct) 1936.

136 Lurie, M. On the Mechanism of Immunity in Tuberculosis, *J Exper Med* **63** 923-946 (June) 1936.

ing organisms and on the general condition of the animal. I am not as convinced as Lurie is of the importance of rapidly mobilized mononuclear cells in destroying tubercle bacilli. No one has yet proved that phagocytosis per se is of great importance in infectious disease.

Bogen¹³⁷ kept guinea-pigs inoculated with tubercle bacilli at a high temperature (85 to 90 F) for long periods to determine the effect of thermotherapy. The animals that were kept warm showed much less extensive tuberculosis after three months than did control animals. Bogen believes these results occurred because heated animals kept quieter, rested more and incidentally reduced the spread of infection to each other.

TYPHOID

In 1936 only 1 death from typhoid per hundred thousand life insurance policy holders was recorded,¹³⁸ as compared with 23 deaths twenty-five years ago. This infection has registered the largest percentage of decline of all causes of death in the given period, yet no satisfactory method of specific therapy has been achieved. The decline is apparently due entirely to preventive measures.

Attempts are still being made to develop specific antiserums. Two papers¹³⁹ dealing with the subject have been published, but the results are not encouraging. Similar unconvincing reports of cases in which serum was used appeared in a paper¹⁴⁰ dealing with "immunotransfusion." In most of the charts designed to illustrate the effectiveness of this form of therapy, the temperature seemed to be declining before the injection of blood.

Gannon¹⁴¹ reports a case illustrating the persistence of typhoid bacilli in persons recovered from typhoid. Bacilli were isolated from an abscess of the sternum nearly six years after recovery from typhoid. In an experimental study¹⁴² "typhoid leukocidin" from typhoid bacilli was found to reduce the number of neutrophilic granulocytes. Its

137 Bogen, E. Thermotherapy in Experimental Tuberculosis, *Proc Soc Exper Biol & Med* **36** 11-16 (Feb) 1937

138 *Statist Bull, Metropolitan Life Ins Co* **18** 4 (Jan) 1937

139 Schwartzman, G., Baehr, G., and Hollingsworth, W. Y. Treatment of Typhoid with an Antitoxic Antityphoid Serum, *Arch Int Med* **58** 799-811 (Nov) 1936. Robertson, R. C., and Yu, H. The Serum Treatment of Typhoid Fever, *Brit M J* **2** 1138-1140 (Dec 5) 1936.

140 Habel, K., and Crocker, W. J. Treatment of Nineteen Cases of Typhoid Fever in Children, *J Pediat* **9** 149-166 (Aug) 1936.

141 Gannon, J. A. Typhoid Abscess About Lower End of Sternum, *J A M A* **105** 113 (July 13) 1935.

142 Dennis, E. W. and Senekjian, H. Typhoid Leucocidin, *Proc Soc Exper Biol & Med* **36** 61-63 (Feb) 1937.

action was neutralized by immune globulin. The leukocidin was believed to be responsible for the leukopenia of typhoid.

Goodpasture¹⁴³ presents new light on the pathogenesis of typhoid. He points out that the primary site and the mechanism of invasion are still unknown. In 1 case studied at necropsy he observed small gram-negative intracellular bacilli in the cytoplasm of plasma cells of the lymphoid follicles of iliac and mesenteric lesions early in the course of the disease. He regards these as typhoid bacilli modified by existence within the cells. He believes, therefore, that the portal of entry is by way of these cells and also by way of the cytoplasm of the large macrophages in which the usual large form of typhoid bacilli are found. The plasma cells may serve as the focus of infection during the period of incubation and also throughout the entire course of the illness. It remains to be proved whether or not the bacillary inclusions are actually viable typhoid bacilli.

Salmonella Supestifer (*Hog-Cholera Bacillus*) Infection.—Numerous observers have presented case reports of this infection. The bacillus was first erroneously associated with "hog cholera" years ago but has since been recognized as a human pathogen. It is a frequent cause of food poisoning but apparently may also reside in the human gastrointestinal tract as a commensal until a lowering of the resistance permits it to become invasive and cause disease. The infection often occurs secondary to other illness and during times of war, famine and exposure. The subject is reviewed by Harvey,¹⁴⁴ who adds data on 21 new cases. The majority of cases occur in children. The infection often resembles typhoid, so that an accurate diagnosis can be made only by isolating the bacillus from the blood and identifying it by means of special bacteriologic methods. Localization¹⁴⁵ in various parts of the body may occur, for instance, as pneumonia, arthritis, meningitis or endocarditis. The mortality rate among patients less than 25 years old was 19 per cent, for those over 25 it was 58 per cent.

Others¹⁴⁶ have reviewed the literature on meningitis caused by bacilli of the *Salmonella* group. For only 19 of the 34 cases reported

143 Goodpasture, E. W. Concerning the Pathogenesis of Typhoid Fever. *Am J Path* **13** 175-185 (March) 1937.

144 Harvey, A. M. *Salmonella Supestifer* Infection in Human Beings, *Arch Int Med* **59** 118-135 (Jan) 1937. Boycott, J., and McNee, J. W. Human Infection with American Hog-Cholera Bacillus, *Lancet* **2** 741-742 (Sept 26) 1936. Frank, T. J. F. *Salmonella* Infections. Report of Sporadic Case of Bacillus Enteritidis (Gartner) Septicemia, *M J Australia* **1** 457-463 (March 27) 1937.

145 Cohen, L., Fink, H., and Gray, I. *Salmonella Supestifer* Bacteremia, with Pericarditis, Pneumonitis and Pleural Effusion, *J A M A* **107** 331-333 (Aug 1) 1936.

146 Bahrenburg, J. H., and Ecker, E. E. Meningitis Due to Organisms Belonging to the *Salmonella* Group. *J Infect Dis* **60** 80-87 (Jan-Feb) 1937.

can positive diagnosis be accepted since in many cases adequate identification was not made

BACILLARY DYSENTERY

Felsen¹⁴⁷ made a follow-up study of 122 patients who had dysentery in an epidemic caused by Flexner bacilli in New Jersey in 1934. About one third of them had recurring diarrhea or bloody stools for a long time thereafter. In 10 per cent chronic ileitis or ulcerative colitis had developed by the end of the first year. In many it appeared that the original attack had merely subsided, never having cleared up completely. Bacilli were still recoverable from a small percentage of patients, but secondary infection of the bowel with enterococci and *Bacillus coli* was common. Felsen calls attention to the importance of recognizing atypical forms with appendicular involvement, distal ileitis and mesenteric lymphadenitis. He reports several cases of dysentery ushered in with symptoms of pneumonia. In a study¹⁴⁸ of dysentery in England, many patients infected with Sonne type did not have the typical symptom of bloody diarrhea. Ulcerative colitis was, however, noted as a sequela. The Shiga type of dysentery was almost never encountered. Bacillary dysentery has apparently been endemic since the fourteenth century. It is continuously renewed by returning tourists who bring back new strains.

Rothman¹⁴⁹ reviews the literature pertaining to dysentery bacillemia and adds a report of a case of his own. Frequently the clinical picture resembles that of typhoid. Diagnosis can be made only by cultivating the organism from the blood and identifying it. Dysentery bacteremia probably occurs more often than is ordinarily believed. Two cases of bacillemia are reported by Haynes¹⁵⁰.

In a paper presented before the Harvard Tercentenary Conference in September 1936 Shiga¹⁵¹ discusses the advances of knowledge of dysentery since his discovery of the causative organism thirty-eight

147 Felsen, J., and Gorenberg, H. Chronic Dysentery, Distal Ileitis and Ulcerative Colitis, *Am J M Sc* **192** 553-556 (Oct.) 1936. Felsen, J. Relationship of Bacillary Dysentery to Distal Ileitis, Chronic Ulcerative Colitis and Non-Specific Intestinal Granuloma, *Ann Int Med* **10** 645-669 (Nov.) 1936, Pneumonic Type of Bacillary Dysentery, *New York State J Med* **37** 253-254 (Feb. 1) 1937.

148 Hurst, A. F., and Knott, F. A. British Dysenteric Infections, *Lancet* **2** 1197-1201 (Nov. 21) 1936.

149 Rothman, P. E. Dysentery Bacillemia, *J Pediat* **9** 167-172 (Aug.) 1936.

150 Haynes, E. A Bacteriologic Study of Forty Cases of Dysentery in Infants and Children, *J Infect Dis* **60** 251-256 (March-April) 1937.

151 Shiga, K. The Trend of Prevention, Therapy and Epidemiology of Dysentery Since the Discovery of Its Causative Organism, *New England J Med* **215** 1205-1211 (Dec. 24) 1936.

years ago He says that it appears most desirable at present to classify the organism into three types, as follows

- I *Bacillus dysenteriae* (Shiga-Kruse)
- II *Bacillus metadysenteriae* (representative strains Flexner, Strong, Y, Ohno and Schmitz)
- III *Bacillus paradysenteriae* (representative strains Kruse-Sonne and Ohara-Mita)

Dysentery endotoxin, he claims, produces an antitoxin, but toxoid treatment has been unsuccessful Antitoxic serum, however, gives good results, especially in cases of mild or moderately severe involvement In cases of severe dysentery in which the toxin has acted on the peristaltic centers in the intestinal wall and paralysis has set in, antitoxin is of no value A mild toxin stimulates peristalsis and causes diarrhea, strong toxin causes paralysis Serum therapy is not effective in type II or type III infections In Japan in recent years it seems that type I, or Shiga, strains have been replaced by type II or type III strains (see also the discussion of changes of type in the concluding paragraphs of this review)

Shiga states that 30 per cent of convalescent patients continue to excrete bacilli for months About 9 per cent of familial contacts were found to be carriers Seventy-five per cent of the patients were less than 10 years of age He mentions the oral administration of vaccine but does not recommend it, because of its nonproved value I believe Shiga's method of classification into three types as types I, II and III is an improvement, but I do not favor the prefixes meta- and para- in bacterial nomenclature

Amebic Dysentery—A complete report of the Chicago outbreak of amebic dysentery has been published by the United States Public Health Service¹⁵²

MISCELLANEOUS INFECTIONS

Tetanus—In further work on tetanus Abel and his associates¹⁵³ studied the distribution and fate of toxin in the body Toxin in excess of a lethal dose accumulates in the blood and lymph, and only a negligible amount is found in the tissue spaces About 90 per cent can be recovered from the blood and lymph, the remainder is irremovably fixed to the tissue cells Toxin which can be recovered from organs of an infected animal is only that which is contained in the blood or lymph

¹⁵² Epidemic Amebic Dysentery The Chicago Outbreak of 1933, Bulletin 166, National Institute of Health, United States Treasury Department, Public Health Service, 1936

¹⁵³ Abel, J J , Evans, E A , and Hampil, B Researches on Tetanus, Bull Johns Hopkins Hosp 59 307-391 (Nov) 1936

An important point in regard to therapy which has emerged from these valuable experiments is the fact that the time of death of infected animals is predetermined. Whether a moderate amount of toxin or a great excess is injected, the actual time of death is definitely determined in each case by the absolute amount which has been irretrievably fixed in the various organs of the body in the first few hours after the requisite threshold concentration in the tissue spaces has been attained. "The events of these early hours initiate the period of incubation, determine its duration, and are decisive for life and death." If this is actually the case in human beings, any hope resting on the present form of antitoxin therapy must be deferred.

Several observers¹⁵⁴ recently analyzed 642 cases of tetanus. Specific antitoxic treatment, they conclude, has accomplished relatively little in the way of saving of life. They believe sedatives constitute the most hopeful form of therapy.

Rickettsial Diseases—Pinkerton¹⁵⁵ warns against inaccurate and unnecessarily complex classification of diseases of this group. He urges that classification be made on the basis of morphologic and histopathologic changes in infected tissues and on immunologic studies rather than on variations in the clinical picture in man and in animals. He presents in tabular form the differences between certain diseases caused by Rickettsia. In another paper,¹⁵⁶ methods for tissue culture for biologic study and classification of Rickettsiae are described.

Lewthwaite and Savoor¹⁵⁷ have published data to show the identity of "rural typhus" of Malaya and tsutsugamushi disease. They suggest that the former term be abandoned. "Urban typhus" of Malaya and Rocky Mountain spotted fever possess a minor degree of reciprocal cross-immunity, but their exact relationship is still undetermined.

Zinsser¹⁵⁸ states that although the mode of transmission of typhus fever is well known, sanitary measures alone are not sufficient to con-

154 Huntington, R. W., Thompson, W. R., and Gordon, H. H. The Treatment of Tetanus with Antitoxin, *Ann Surg* **105** 93-96 (Jan.) 1937.

155 Pinkerton, H. Criteria for the Accurate Classification of the Rickettsial Diseases (Rickettsioses) and of Their Etiological Agents, *Parasitology* **28** 172-188 (March) 1936.

156 Pinkerton, H. The Application of Tissue Culture to the Morphological and Biological Study and Classification of Rickettsiae, *Arch f exper Zellforsch* **18** 343-359, 1936.

157 Lewthwaite, R., and Savoor, S. R. The Typhus Group of Diseases in Malaya. Relation of Rural Typhus to Tsutsugamushi Disease with Special Reference to Cross Immunity Tests, *Brit J Exper Path* **17** 448-460 (Dec.) 1936, Typhus Group of Diseases in Malaya. Relation of Tsutsugamushi Disease (Including Rural Typhus) to Urban Typhus, *ibid* **17** 461-472 (Dec.) 1936.

158 Zinsser, H., and Macchiavello, A. Further Studies on Typhus Fever, *J Exper Med* **64** 673-687 (Nov.) 1936.

trol epidemics. He suggests mass vaccination with rickettsial cultures treated with solution of formaldehyde, which can now be made on a large scale. Attempts to produce immunity in guinea-pigs with sero-vaccination (mixtures of virulent defibrinated guinea-pig blood and convalescent serum) were successful.

Dengue—Dengue, ordinarily regarded as an exotic disease, is as a matter of fact prevalent in the southern part of the United States. In 1934, for instance, 10,000 cases were recorded in Florida. Griffiths and Hanson¹⁵⁹ review the problem and bring out a number of interesting points. The disease in the United States is transmitted only by the *Aedes Aegypti* mosquito. To become infective the mosquito must secure blood from a patient in the first forty-eight hours of the initial fever. The mosquito is then noninfectious for about twelve days (extrinsic incubation period), but after this time it is infectious for the duration of its life. The intrinsic incubation period in man lasts for from four to ten days. When an epidemic breaks out, the disease is spread from person to person with great rapidity, second only to that of influenza. In Galveston, for example, about 60 per cent of the population suffered attacks in 1932. In Athens, Greece, 239,000 cases were reported in the 1928 epidemic. Warm wet weather favors the multiplication of the mosquitoes which spread the disease.

Allusion has been made to the similarity in the epidemiological characteristics of dengue and yellow fever and of the ever present danger of an outbreak of the latter disease if conditions become favorable.

Cheney¹⁶⁰ reports 20 cases of "dengue-like fever" in California. The disease frequently exhibited a course of biphasic fever. Identity with true dengue was not established.

Pleurodynia—Two outbreaks of pleurodynia have been recognized for the first time in the middle western states.¹⁶¹ The one observed in Ohio involved at least 282 persons. Many more, unreported, cases are presumed to have existed. The epidemic began in June, reached its height in August and disappeared in October. Children and young adults were chiefly affected. The contagiousness of the disease was indicated by its appearance in twenty-four groups of "contact cases." The disease, as in other epidemics reported previously, was characterized by severe pain in the region of the diaphragmatic attachment to the thorax.

159 Griffiths, T. H. D., and Hanson, H. Significance of an Epidemic of Dengue, *J. A. M. A.* **107** 1107-1110 (Oct. 3) 1936.

160 Cheney, G. A Dengue-Like Fever, *California & West Med.* **46** 8-11 (Jan.) 1937.

161 Welborn, M. B. Epidemic Pleurodynia, *Am. J. M. Sc.* **191** 673-678 (May) 1936. Harder, F. K. Epidemic Myalgia or Pleurodynia in Southwestern Ohio, *ibid.* **191** 678-685 (May) 1936.

Nerve Infections—Davis¹⁶² reports an unusual disease in 10 children. It was characterized by a segmental distribution of pain, often with hypesthesia and hyperalgesia, which followed other infections, particularly of the respiratory tract. He suggests that a neurotropic virus, probably activated by the preceding infection, attacked the posterior spinal nerve roots and their ganglions. The disease may be regarded as a form of herpes zoster, since vesiculation occurred in 2 cases. A review of the literature revealed other similar observations.

Another comparatively rare neurologic disease, acute infective polyneuritis, is discussed by Pinckney,¹⁶³ of England. The causative virus, it is claimed, has been isolated and passed through monkeys. The infection is classified into three types: one, afebrile, with painless peripheral neuritis with rapid onset; the second, with fever, peripheral polyneuritis, facial paralysis and slight general bulbar weakness; the third, with ascending polyneuritis and involvement of the muscles of respiration, simulating Landry's paralysis.

Yellow Fever—Soper¹⁶⁴ sums up the knowledge recently gained about the epidemiology of yellow fever. A decade ago yellow fever was believed to have been exterminated in South America, only to crop up again and again in the subsequent years to the disillusionment of interested epidemiologists. The disease was found to be widespread after the introduction of the viscerotome¹⁶⁵ to obtain hepatic tissue without necropsy by which positive identification of yellow fever can be made by histologic examination. Furthermore, it soon became obvious that the mode of transmission of infection concerned other means beside the *Aedes Aegypti* mosquito, which formerly was believed to be solely responsible, since cases were noted in persons in regions where this mosquito was not present. This newly recognized form of the disease, called "jungle yellow fever," is endemic and permanent, in contrast with the mosquito-transmitted form, which flares up and dies out in scattered areas. The viruses of these infections are believed to be identical. The source of the disease is still unknown, although immunity tests reveal protective substances in the blood of opossums and monkeys, suggesting that these and other animals may serve as reservoirs of infection.

162 Davis, J. H. Segmental Neuralgia in Children Simulating Visceral Disease, *J. A. M. A.* **107** 1620-1625 (Nov. 14) 1936.

163 Pinckney, C. Acute Infective Polyneuritis, *Brit. M. J.* **2** 333-335 (Aug. 15) 1936.

164 Soper, F. L. The Newer Epidemiology of Yellow Fever, *Am. J. Pub. Health* **27** 1-14 (Jan.) 1937.

165 Rickard, E. R. The Organization of the Viscerotome Service of the Brazilian Cooperative Yellow Fever Service, *Am. J. Trop. Med.* **17** 162-190 (March) 1937.

Leishmaniasis—The search in the western hemisphere for diseases related to Old World kala-azar has continued since Darling's investigation in 1906. More recently De Monbreun isolated an organism from a patient with histoplasmosis in the southern part of the United States. He regards the organism as a fungus rather than a protozoan parasite. There is, however, still a question of the possible relationship of this organism to the *Leishmania* group.

In the course of investigation by the viscerotome service of the Rockefeller Foundation in Brazil for the detection of yellow fever, eighty-five specimens of liver containing *Leishmania* bodies were encountered by Penna. After this observation Chagas¹⁶⁶ made a study of the disease caused by these organisms and found it to correspond closely with typical kala-azar in regard to clinical course, laboratory tests and histologic lesions. The disease occurs throughout the northern and eastern parts of Brazil and in the Chaco territory of the Argentine. Fifty-three per cent of cases occurred in children less than 6 years of age. Antimony derivatives were of value in the treatment.

Several French investigators¹⁶⁷ have had success in diagnosing kala-azar by making sternal or tibial puncture rather than splenic puncture to obtain material for study. The former method, they say, is less dangerous and is especially useful in the case of infants.

Schistosomiasis—Exotic diseases are easily missed by physicians not familiar with them. It is always important to bear them in mind in dealing with a person recently arrived from other portions of the world, especially in the case of certain infections, such as kala-azar and schistosomiasis, in which specific therapy may save the patient's life. A case of imported schistosomiasis was studied by Hoff¹⁶⁸. The symptoms were those of cirrhosis of the liver with ascites and 50 per cent eosinophils. Therapy with antimony and potassium tartarate was apparently begun too late for the patient died. A second patient, a carrier, was freed from parasites with a trivalent sodium antimony compound (fuadin).

Actinomyces—Physicians are likely to acquire certain mental associations in therapeutics which are difficult to alter. An example is the fungous infection-potassium iodide complex which arose on an empirical

166 Chagas, E. Visceral Leishmaniasis in Brazil, *Science* **84** 397-398 (Oct 30) 1936

167 Lorando, N. Sternal Puncture in Leishmaniasis, *Bull et mem Soc med d hôp de Paris* **53** 314-316 (March 8) 1937. Giraud, P, and Gaubert. Value of Bone Marrow Puncture for Diagnosis of Mediterranean Kala Azar, *ibid* **53** 336-339 (March 15) 1937.

168 Hoff, A. Schistosomiasis. Report of Two Cases, *J A M A* **107** 1375-1378 (Oct 24) 1936.

basis years ago To my knowledge the iodides have never been proved to be of specific value in fungous infections Wangensteen¹⁶⁹ reviewed a number of cases of actinomycosis and says he was unable to note any benefit whatever from these salts The effects of irradiation are also discussed without enthusiasm The treatment of choice is the surgical removal of infected material, when possible, and the curettage and evacuation of dead tissue in the visceral forms Thymol therapy has recently been recommended¹⁷⁰

Appendicitis—Wangensteen and Bowers¹⁷¹ briefly discuss the literature in regard to the etiology of appendicitis and add their own experimental observations Obstruction and infection are the two most important causative factors experimentally in the dog Obstruction was always followed by inflammation, obstruction of an appendix previously washed out was usually well tolerated, and infection without obstruction did not produce inflammation Appendical concretions were the acutely obstructing agent in most instances of perforated appendix in man

Rabies—Webster and Clow¹⁷² and Kanazawa¹⁷³ cultivated rabies virus in vitro Tissue culture virus vaccine is safer than brain or spinal cord substance containing the virus, since the superfluous animal tissue may in itself cause paralysis or secondary infection In another study¹⁷⁴ the presence of neutralizing antibodies in mice failed to guarantee the existence of immunity A surprising observation was that vaccine containing no demonstrable living virus produced resistance It is generally believed that the injection of dead filtrable virus does not confer immunity Rabies virus may be an exception to the rule

Vincent's Stomatitis—Farrell and McNichols¹⁷⁵ made a critical study of the value of various forms of treatment of stomatitis that

169 Wangensteen, O H The Role of Surgery in the Treatment of Actinomycosis, *Ann Surg* **104** 752-770 (Oct) 1936

170 Myers, H B Thymol Therapy in Actinomycosis, *J A M A* **108** 1875 (May 29) 1937

171 Wangensteen, O H, and Bowers, W F An Experimental Study of the Significance of the Obstructive Factor in the Genesis of Acute Appendicitis, *Tr West S A* **45** 195-252, 1935

172 Webster, L T, and Clow, A D Propagation of Rabies Virus in Tissue Culture and Successful Use of Culture Virus as an Antirabic Vaccine, *Science* **84** 487-488 (Nov 27) 1936

173 Kanazawa, K In Vitro Culture of Rabies Virus, *Jap J Exper Med* **15** 17-28 (Feb) 1937

174 Webster, L T Diagnostic and Immunological Tests of Rabies in Mice, *Am J Pub Health* **26** 1207-1210 (Dec) 1936

175 Farrell, G W, and McNichols, W A Efficacy of Various Medicaments in the Treatment of Vincent's Stomatitis, *J A M A* **108** 630-633 (Feb 20) 1937

is believed by some to be caused by fusiform and spiral organisms. Nearsphenamine, chromium trioxide, ultraviolet rays, aconite, iodine, chloroform, potassium arsenite, aniline dyes and other remedies were found to be without value. They observed the development of Vincent's disease in 6 patients under intensive treatment with nearsphenamine for syphilis, an occurrence previously observed by others. The most effective method of treatment included oral hygienic measures, removal of mechanical irritation, abstinence from tobacco and avoidance of surgical treatment of the mouth. Solution of hydrogen peroxide U S P favored the cure of the infection when used as a mouthwash.

Thrombo-Angitis Obliterans—Allen and Lauderdale¹⁷⁶ briefly review certain experiments designed to demonstrate the infectious nature of thrombo-angitis obliterans. The results in general were inconclusive, yet the disease seems to be infectious in origin. The authors describe the case of a surgeon who six months previous to observation had amputated the toe of a man with the disease. During the operation the palmar surface of the surgeon's third finger was accidentally pierced by a spicule of bone. Although no local lesion was noted, a month later changes in color, consisting of cyanosis and pallor on exposure to cold, developed in the injured finger. Several weeks later similar changes occurred in other fingers of the same hand. The symptoms diminished somewhat but had not disappeared entirely. A diagnosis of thrombo-angitis obliterans was made. The possibility of coincidental development of the disease was considered, but the local development of the condition after a definite history of injury with possibly infective material strongly suggested the infectious nature of the disease.

Bacteroides Funduliformis Infection—Attention is called¹⁷⁷ to this unusual form of infection, which was observed in 6 cases. It occurs most often in patients with necrotic ulcerating carcinoma of the bowel. The organisms frequently invade the blood, hepatic abscesses were found in all fatal cases. The infection should be suspected when icterus appears in the type of patient mentioned. The authors also review the literature on the subject.

Toxoplasmosis—Toxoplasma, a protozoan parasite of various mammals and birds, has been described in various parts of the world but has been almost unnoticed in North America. The organism, like certain viruses, grows only within living cells, but it has been cultivated

¹⁷⁶ Allen, E V, and Lauderdale, T L. Accidental Transmission of Thrombo-Angitis Obliterans from Man to Man, Proc Staff Meet, Mayo Clin **11** 641-644 (Oct 7) 1936.

¹⁷⁷ Dixon, C F, and Deuterman, J L. Postoperative Bacteroides Infection, J A M A **108** 181-185 (Jan 16) 1937.

in vitro with chick embryo¹⁷⁸ It is virulent for mice, guinea-pigs and rabbits, in monkeys it causes febrile, nonfatal disease Some years ago Bland, in England, induced toxoplasmosis in rabbits into which had been injected blood from patients with infectious mononucleosis It was uncertain whether the toxoplasma was the cause of the human disease or whether the organism was harbored in the rabbit as a commensal

MISCELLANEOUS STUDIES

Air-Borne Infection—Statement was made in a preceding paragraph of the remarkable decline in the incidence of typhoid, to which may be added other infections of the gastro-intestinal tract This has largely been brought about by the control and prevention of contamination of food and drink One might contrast this achievement with the unchanged incidence of infections known to be air borne, such as the common cold, influenza, pneumonia, meningitis and others, which together are responsible for 85 per cent of deaths from infectious disease A reduction of these diseases might be anticipated should methods be developed to sterilize the air The magnitude of such a problem is obvious In two papers presented at the Harvard Tercentenary in August 1936, W F Wells and M W Wells¹⁷⁹ point out that under conditions of living in enclosed rooms persons are inhaling one another's nasopharyngeal flora as once they ingested each other's intestinal flora in food and water supplies In ingenious experiments these investigators developed an apparatus to spray organisms into the air and another to centrifugate the air so as to concentrate bacteria and viruses contained therein for tests They studied the length of time during which droplets of varying size containing bacteria remain suspended in the air and tested the viability of floating organisms For example, *H influenzae* died in one hour, whereas staphylococci, pneumococci, streptococci and diphtheria bacilli remained viable for several days Organisms of the "intestinal group" seldom survived more than eight hours The virus of influenza when sprayed into the air could be recovered up to an hour by centrifugation

In tests to determine measures which may serve to sterilize air, ultraviolet irradiation with a quartz mercury vapor lamp was most effective Air contaminated with known bacteria was passed at definite distances through ultraviolet rays Organisms which divide in one plane, such as streptococci and pneumococci, were easily destroyed, but

178 Sabin, A B, and Olitsky, P K Toxoplasma and Obligate Intracellular Parasitism, *Science* **85** 336-338 (April 2) 1937

179 Wells, W F, and Brown, H W Recovery of Influenza Virus Suspended in Air, *Science* **84** 68-69 (July 17) 1936 Wells, W F, and Wells, M W Air-Borne Infection, *J A M A* **107** 1698-1703 (Nov 21) 1936, Air-Borne Infection Sanitary Control, *ibid* **107** 1805-1809 (Nov 28) 1936

the outer layers of cocci which grow in clumps protected the inner ones from the rays. The virus of influenza was easily destroyed.

The importance of studies such as these can hardly be overestimated, since they suggest definite lines of attack on the spread of air-borne infectious diseases.

Mandelic Acid Therapy—After so many disappointments in the field of chemotherapy for infections due to bacterial diseases, it is but natural to regard the introduction of any new substance with skepticism. It is surprising, therefore, that within a year or two two substances were proposed, sulfanilamide and mandelic acid, both of which appear to have real merit. Only further work can tell if either is as valuable as early reports indicate. Mandelic acid has been the subject of numerous published articles,¹⁸⁰ a few of which are referred to here. The development and use of the drug were based on the observations of Shohl and Janney, who demonstrated the importance of a low hydrogen ion concentration of the urine in combating infections due to colon bacilli, and of Clark and Helmholtz, who developed the ketogenic diet. After Fuller showed that beta-hydroxybutyric acid was an important factor of this treatment, Rosenheim, in England, suggested the use of mandelic acid, which produced a condition in the urine similar to that which resulted from the use of the unpleasant ketogenic diet.

Most of the papers thus far published on the subject are favorable to its use. It is emphasized, however, that before benefit can be expected therefrom, any existing obstructive lesions must be corrected and free drainage established. Thus far the effects obtained by the proper use of the mandelic acid and proper acidity of the urine are said to indicate the superiority of this drug to all other forms of medication of urinary infections. It is important, however, to establish the etiologic diagnosis in all cases before treatment, since the drug is apparently specific only for infections caused by colon bacilli. Little or no beneficial effect was obtained in infections due to *Bacillus proteus*, *Bacillus pyocyaneus* or the staphylococcus.

Antiseptics—Nye¹⁸¹ calls attention to the absurdity of the variety of antiseptics in common use at present, few of which have actual

180 Rosenheim, M. L. Mandelic Acid in the Treatment of Urinary Infections, *Lancet* **2** 1083-1087 (Nov 7) 1936. Helmholtz, H. F., and Osterberg, A. E. Rate of Excretion and Bactericidal Power of Mandelic Acid in the Urine, *J. A. M. A.* **107** 1794-1796 (Nov 28) 1936. Carrol, G., Lewis, B., and Kappel, L. Mandelic Acid as a Urinary Antiseptic, *ibid.* **107** 1796-1799 (Nov 28) 1936. Cook, E. N., and Buchtel, H. A. Mandelic Acid in the Treatment of Infections of the Urinary Tract, *ibid.* **107** 1799-1800 (Nov 28) 1936. Dolan, L. P. Experience with Ammonium Mandelate in Urinary Infections, *ibid.* **107** 1800-1805 (Nov 28) 1936.

181 Nye, R. N. The Relative in Vitro Activity of Certain Antiseptics in Aqueous Solution, *J. A. M. A.* **108** 280-287 (Jan 23) 1937.

value Tests were made in vitro for the purpose of measuring certain qualities that seemed most desirable in antiseptics used for the treatment of wounds, cuts, abrasions or irritations Solutions containing iodine, mercury, chlorine and other chemicals were tested Of all antiseptics studied, compound solution of iodine U S P possessed more of the desirable qualities of effectiveness, with low cost, than any of the other antiseptics tested

Lyophile Serum—Mudd and his associates¹⁸² report their studies on the preservation of serum by drying in vacuo By means of this technic human serum (convalescent serum) can be collected at times of epidemics and preserved in the dry state for future use When serum is desired for use, the dried porous mass can be redissolved in a volume of liquid smaller than the original one, which permits a fourfold concentration In another paper¹⁸³ the results of clinical use of lyophile serums in various diseases is reported The results compare favorably with those of other serums when used in the prophylaxis of scarlet fever, measles, mumps, whooping cough and German measles and in the treatment of scarlet fever, mumps, erysipelas, whooping cough and infections with hemolytic streptococci

Circulatory Failure in Infectious Disease—A brief but valuable discussion of the rational treatment of circulatory failure in infections is given by Eggleston¹⁸⁴ He points out the ineffectiveness of most of the drugs used in the hope of stimulating the heart and outlines the procedure most likely to be beneficial

Crystalline Virus—Stanley¹⁸⁵ presented more evidence before the American Association for the Advancement of Science to support the view that the crystalline substance previously reported on was the actual cause of tobacco mosaic disease and not merely carried over with minute amounts of still unrecognized virus With the newly developed technic of ultracentrifugation at tremendous speed and the knowledge that the crystalline protein previously isolated was of high molecular weight, studies were made of other plant diseases presumably of "virus" origin As a result a new crystalline protein was isolated from tobacco plants

182 Mudd, S , Flosdorf, E W , Eagle, H , Stokes, J , and McGuinness, A C The Preservation and Concentration of Human Serum for Clinical Use, J A M A **107** 956-959 (Sept 19) 1936

183 McGuinness, A C , Stokes, J , and Mudd, S The Clinical Uses of Human Serums Preserved by the Lyophile Process, J Clin Investigation **16** 185-196 (March) 1937

184 Eggleston, C Drugs Used in the Treatment of Circulatory Failure in Acute Infectious Diseases, J A M A **107** 1213-1215 (Oct 10) 1936

185 Stanley, W M , and Wykoff, R W G The Isolation of Tobacco Ring Spot and Other Virus Proteins by Ultracentrifugation, Science **85** 181-183 (Feb 12) 1937

with ring spot disease which differed from the virus of mosaic disease. By similar methods there were isolated a number of other less stable plant viruses which in respect to concentration in the host and to instability were more like certain animal viruses than the abundant and easily manipulated mosaic virus.

Relation of Cancer to Virus Diseases—Investigators are confronted with a question of great importance as to whether viruses actually cause cancer or whether, like other substances, such as coal tar, they simply provoke some perversion of the internal chemistry of cells which results in cancer. The subject is adequately reviewed by Rous¹⁸⁶ in a Harvey Lecture and needs no further comment here except for brief reference to subsequent contributions.

Murphy¹⁸⁷ is opposed to the view that viruses cause cancer. The only proved relationship, he believes, is that a virus may initiate changes leading to a malignant process, and it has no part in the formal genesis of neoplasms.

Most fowl tumors, except certain ones induced chemically, are transmissible by cell-free filtrates. Those transferable only by grafts of living tumor cells more closely resemble mammalian tumors in this respect. Claude¹⁸⁸ believes that the difficulty of establishing transferred growth in certain cases was due to the presence of some inhibiting factor rather than to the absence of the agent. He found, for instance, that an inhibiting agent could be separated from the tumor-inducing filtrate of a certain chicken tumor by high speed centrifugation, and he applied this method to fowl fibrosarcoma. Tumors developed when the sediment alone was injected into chickens but not if the unspun filtrate was used. He then mixed some of the sediment with its own supernatant fluid and thereby again made the filtrate inert. This indicates that the tumor-forming agent is active only when separated from the neutralizing element. Repetitions of these experiments have thus far failed to show similar results with mammalian tumors. Other investigators have gathered evidence to weaken the theory of the relationship of filtrable viruses to tumor formation. Jobling and Sproul¹⁸⁹ report their studies in which distinct differences were noted between the active agent of the Rous chicken sarcoma and two diseases of virus origin, namely, vaccinia and tobacco mosaic disease. In experiments

186 Rous, P. The Virus Tumors and the Tumor Problem, *Am J Cancer* **28** 233-272 (Oct) 1936.

187 Murphy, J. B. Relation of Filtrable Viruses to Malignant Disease, *Proc Staff Meet, Mayo Clin* **11** 789-790 (Dec 9) 1936.

188 Claude, A. Preparation of an Active Agent from Inactive Tumor Extracts, *Science* **85** 294-295 (March 19) 1937.

189 Jobling, J. W., and Sproul, E. E. Relation of Certain Viruses to the Active Agent of the Rous Chicken Sarcoma, *Science* **85** 270-271 (March 12) 1937.

involving the use of both protein and lipid fractions of extracts causing these three diseases the authors were able to produce sarcoma with the lipid extract only. The inability to produce disease with the lipid extract of the known viruses indicates that they are of a different chemical nature. The authors believe that the agent causing chicken sarcoma is not a virus but a product of abnormal cell metabolism, which when injected into normal animals may stimulate normal cells to make a similar substance and thus perpetuate the disease. It is of interest to note how closely this theory resembles the facts associated with the transformation of types of pneumococci, in which any of the nonspecific S forms of pneumococci may be transformed into various specific M types by incubating the S forms together with the heat-killed M forms of the desired type. The question seems to involve the fascinating problem of the transformation of biologic types involving filterable viruses, bacteria and tissue cells.

Transformation of Biologic Types—A feature characteristic of scientific development is the theoretical discussion of a subject for years which seems to culminate suddenly in the publication of a number of papers confirming the theory. This has taken place in regard to the transformation of biologic types. The probable mutation of smallpox virus to vaccinia virus and of "street" virus to "fixed" virus of rabies has long been suspected. One may recall experiments with tissue cultures in which monocytes changed into fibroblasts. Numerous observers have suggested that mutation may play a rôle in the changing of types of gonococci or meningococci and among the colon-typhoid group of bacilli. The artificial induction of a change of type specificity among pneumococci is well known. More recently Mooser has caused one variety of typhus organisms to change into another. Andrewes and Smith¹⁹⁰ noted a sudden increase in the virulence of influenza virus in the course of passage through mice. The change is ascribed to the appearance of a mutant form, which thereafter gradually replaced the original form. Andrewes,¹⁹¹ working with a virus of rabbit fibroma isolated by Shope, found that the virus in his hands no longer produced tumor-like growths when injected into rabbits but gave rise to acute inflammatory lesions. Evidence is presented that the original tumor-forming strain and the inflammatory strain produced cross-immunization and that one was not a contamination or separate strain but apparently a mutant form of the other.

190 Andrewes, C. H., and Smith, W. Influenza. Further Experiments on the Active Immunization of Mice, *Brit. J. Exper. Path.* **18** 43-55 (Feb.) 1937.

191 Andrewes, C. H., and Shope, R. E. A Change in Rabbit Fibroma Virus Suggesting Mutation, *J. Exper. Med.* **63** 179-184 (Feb.) 1936.

Recently more evidence has been published¹⁹² recording one of the first proved observations on the spontaneous transformation of bacterial types in vivo and in vitro. A strain of *Micrococcus tetragenus* isolated from the blood of a patient was observed over a period of three years under various adverse circumstances of growth. Four different type-specific strains were derived from the original white variety obtained from the patient. The five types were characterized by distinct and constant biologic characteristics involving the production of pigment and serologic specificity. From each of the types, culture phases of the mucoid, smooth and rough forms were derived. One type was observed to change into another in the animal body and on culture mediums. In another study¹⁹³ I attempted to determine the significance of this biologic change of type. The several types were grown under various conditions unfavorable to the growth and life of the organism. Under certain conditions of acidity and heat one group of variants survived, while the second group survived a degree of alkalinity and cold which prevented growth of the other. It appeared that type variation permitted the existence of a strain of bacteria under a wide range of environmental conditions. I believe that evidence of selection, as just described, might explain to some extent what is meant by "virulence." For instance, a variant form of a given organism which finds conditions in the animal body suitable for its growth might be regarded as "virulent." Spontaneous type transformation or mutation may help to explain obscure questions of the origin of certain infectious diseases or of epidemics.

An unsolved problem of great importance involves the forces which cause type transformation or mutation. Chemical changes are believed to be responsible. The subject was discussed by S. P. Reimann¹⁹⁴ at the Wisconsin Cancer Conference as follows:

Mutation has been observed in all species of plants and animals in which a sufficient number of individuals have been observed. In undifferentiated cells there are present many more chemical compounds with open bonds than are present in differentiated cells. These open bonds have innumerable possibilities of chemical combination. It is known that the potency of any undifferentiated cell is more than its realization. Which of its numerous potencies it displays depends upon the environment. In terms of chemistry, which of the open bonds and with what groups they are combined depends upon the chemical molecules, atoms, ions, or radicals offered by the environment, all of course, subject to the guidance of the inherited species specificity.

192 Reimann, H. A. Bacterial Type Transformation, *Proc Soc Exper Biol & Med* **35** 64-65 (Oct) 1936, Bacterial Type Transformation. IV. *Micrococcus Tetragenus* Infection, *J Bact* **33** 499-511 (May) 1937.

193 Reimann, H. A. The Significance of Bacterial Variation. V. *Micrococcus Tetragenus* Infection, *J Bact* **33** 513-523 (May) 1937.

194 Reimann, S. P. The Biology of the Cancer Cell, *Proc Wisconsin Cancer Conf*, to be published, 1937.

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CLINICAL COURSE AND TREATMENT OF SPRUE

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Job, chap 30, verse 27 "My bowels boiled, and rested not, the days of affliction prevented me"

Job, chap 32, verse 19 "Behold, my belly is as wine which hath no vent, it is ready to burst like new bottles"

Tropical sprue as a medical problem is confined to certain sharply delineated geographic areas. As a problem in pathologic physiology, however, the disease has been shown in recent years to be of considerable general importance and interest. The recent reviews of Castle, Rhoads, Lawson and Payne,¹ of Fairley² and of Reed³ have all dealt at length with the history and symptomatology of tropical sprue. Consideration of these reports, however, reveals that a certain difference of opinion exists as to the most effective means of treating sprue and indeed as to the basic mechanism of the disease process. The patients reported on by Reed and by Fairley were treated both by dietary means and by the administration of liver extract, whereas those reported on by Castle and his associates were treated uniformly with liver extract alone, but they were followed for too short a time to allow accurate estimations of the effect of therapy.

A clinical study of thirty-three patients with sprue has been made in this hospital during the past four and a half years. Information is available concerning twenty-nine of these patients over periods varying from three months to four and a half years after they were discharged from the institution. The salient facts concerning these patients both during hospitalization and after their discharge are presented in this report.

From the Hospital of the Rockefeller Institute for Medical Research

1 Castle, W B, Rhoads, C P, Lawson, H A, and Payne, G C. Etiology and Treatment of Sprue, *Arch Int Med* **56** 627 (Oct) 1935

2 Fairley, N H. Tropical Sprue with Special Reference to Intestinal Absorption, *Brit M J* **1** 1176, 1936, *Tr Roy Soc Trop Med & Hyg* **30** 9, 1936

3 Reed, A C. Sprue, a Clinical Summary, *Am J Trop Med* **16** 499, 1936

MATERIAL

All except four of the thirty-three patients studied had resided in tropical or subtropical countries, eleven had lived in China, nine in Puerto Rico, four in Central or South America and one each in Cuba, Turkey, Algeria, Japan and the Philippine Islands. Twenty-five of the patients were females, and eight were males.

In this report the patients have been divided into three groups according to the presence or absence of certain symptoms and clinical findings at the time of the patients' admission to this hospital. All the patients gave histories which were characteristic of sprue, but in this report the histories are disregarded as far as the grouping is concerned. Group A includes those patients who presented the classic picture of severe sprue when first admitted to the hospital, all of them had diarrhea, gastro-intestinal distress and well marked anemia. Group B is made up of those patients who suffered from diarrhea and gastro-intestinal distress but showed no significant degree of anemia. Group C comprises those who presented neither diarrhea nor anemia when they came under observation but complained only of abdominal discomfort and distention.

Group A Patients with Anemia and Diarrhea on Entry—Ten patients presenting the classic picture of severe tropical sprue make up this group. Eight had resided in tropical or subtropical countries, but the other two had never been south of Florida or Texas, respectively. The clinical pictures presented by the last two patients differed in no respect from those seen in the others of the group.

Gastro-Intestinal Symptoms (Table 1) Recurrent disturbances of the gastro-intestinal tract had been present for periods varying from four to twenty years. The most prominent and the most distressing of these symptoms was diarrhea, which had occurred in all the patients. Vomiting had been a prominent feature at one time or another in six of the patients, while nausea was a complaint common to the entire group. Abdominal distention and discomfort had occurred in all.

At the time of the patient's admission to the hospital the stools varied in number from four to twenty per day and were in general voluminous and yellow, with a yeasty odor. In certain instances, however, they were watery and not to be distinguished from any other diarrheal stool. Besides the diarrhea these patients complained of abdominal discomfort associated with cramps, flatulence, distention, bloating and the evacuation of gas.

Loss of Weight (Table 2) Nine of the patients had lost weight over periods of from one to sixteen years. The amount of weight lost varied from 13.6 to 53.6 Kg., and all nine patients were markedly emaciated when admitted. After treatment six patients gained weight rapidly, the weight of one patient being increased by 15 Kg. in less than six weeks.

Oral Symptoms (Table 3) Recurrent soreness of the tongue and mouth had been noticed by nine of these patients over periods varying from one to fifteen years. In most instances the onset of the oral symptoms took place some time after the onset of the gastro-intestinal symptoms. Two types of soreness of the mouth were reported. One type consisted of redness and burning of the tongue and the other of ulceration of the buccal and gingival mucous membrane, accompanied

TABLE 1—*Gastro-Intestinal Symptoms*

Case	Patient	Sex	Before Entry into Hospital				At Entry	
			Vomiting	Flatulence	Diarrhea	Years Before Entry	Flatulence	Diarrhea
Group A								
1	R D	F	+	-	+	7	+	+
2	M F	F	+	+	+	4	+	+
3	M G	F	+	+	+	18	+	+
4	B M	F	+	+	+	7	+	+
5	L N	F	+	+	+	20	+	+
6	G M	M	0	+	+	16	+	+
7	E M	F	+	+	+	9	+	+
8	O O	F	0	+	+	20	+	+
9	L S	F	0	+	+	15	+	+
10	R S	F	0	+	+	7	+	+
Group B								
11	M B	F	+	+	+	4	+	+
12	R B	M	+	+	+	9	+	+
13	A D	F	0	+	+	2½	+	+
14	F E	F	0	+	+	1	+	+
15	M L	F	0	+	+	11	+	+
16	P M	M	0	+	+	8	+	+
17	M P	M	0	+	+	1½	+	+
18	E R	F	0	+	+	6	+	+
19	H W	M	0	+	+	1	+	+
Group C								
20	R C	M	0	+	+	1	+	0
21	A DeG	F	0	+	+	3	+	0
22	R F	F	0	+	+	15	+	0
23	F H	F	+	+	+	24	+	0
24	L H	F	0	+	+	2	+	0
25	P K	M	0	+	+	13	+	0
26	G L	M	0	+	+	3	0	0
27	E P	F	+	+	+	5	0	0
28	R P	F	0	+	+	7	0	0
29	M P	F	+	+	+	12	+	0
30	E P	F	+	+	+	6	+	0
31	B R	F	+	+	+	25	+	0
32	E S	F	0	+	+	8	+	0
33	A W	F	0	+	+	1	+	0

at times with pain and burning of the whole oral cavity. Salivation was frequently a distressing symptom.

At the time of admission to the hospital nine of the patients had visible oral lesions, which consisted of (1) atrophy of the lingual papillae, (2) redness of the tongue and oral mucosa and (3) vesicular and ulcerated lesions of the tongue and mucous membrane. These various types of oral lesions occurred singly or in any combination. Six patients in this group had atrophic glossitis, one of these had aphthous lesions of the tongue, and another had similar lesions of the oral mucosa.

Redness of the tongue was present in three patients, one of these showed also reddening of the oral mucosa, and two of them had aphthae as well

Gastric Analysis (Table 4) A standard method of gastric analysis was employed, consisting of the withdrawal of four specimens of gastric juice. The first specimen was taken from the stomach during fasting, the second twenty minutes after an alcohol test meal, the third forty minutes after the alcohol meal and the fourth twenty minutes after the

TABLE 2—*Loss of Weight*

Case	Loss of Weight, Kg	Duration of Symptoms	Weight at Entry, Kg	Weight at Discharge, Kg
Group A				
1	+	7 years	41.5	54.9
2	53.6	4 years	42.0	57.0
3	13.6	5 years	45.2	42.0
4	+	7 years	55.9	52.4
5	43.2	15 years	52.5	55.7
6	+	16 years	45.9	48.6
7	22.4	1 year	31.4	42.4
8	0		68.7	68.0
9	21.8	3 years	35.4	37.3
10	17.3	7 years	43.7	43.1
Group B				
11	9.1	4 years	44.7	45.7
12	+	9 years	63.8	63.6
			69.8	71.4
13	18.2	2½ years	58.3	56.8
14	+	11 months	48.4	49.0
15	0		55.0	56.7
16	0		70.6	70.2
17	+	14 months	50.1	49.9
18	0		65.7	67.4
19	+	1 month	56.8	57.6
Group C				
20	0		76.2	
21	+	3 years	51.9	53.0
22	0		60.4	61.5
23	4.6	2 years	56.4	56.7
24	12.3	2 years	49.0	50.1
25	13.6	3 years	59.7	59.8
26	13.6	3 years	93.2	89.2
27	0		73.2	
28	+	14 months	50.1	49.9
29	0		61.5	62.4
30	+	6 years		
31	9.1	10 years	41.9	42.7
32	0		52.2	
33	18.2	2 years		

* The patient was admitted to the hospital on two different occasions

intramuscular injection of 0.5 mg. of histamine. In table 4 the volume of gastric juice obtained and the amount of free hydrochloric acid present in each specimen are tabulated.

Failure of the stomach to secrete free hydrochloric acid after the injection of histamine was observed in only one patient (case 6). In four other patients free hydrochloric acid was absent until after the injection of histamine. In only one patient (case 10) was the amount of free hydrochloric acid greater than 30, and in most instances the volume of gastric juice obtained was small.

Blood Picture (Table 5) Nine of the patients gave a history of having had anemia before admission to the hospital. In one instance the anemia had been present for ten years before entry, but in the other cases it was of more recent origin. The exact nature of the type of anemia which was present before admission was unknown except for

TABLE 3—*Oral Symptoms*

Case	Sore Tongue	Sore Mucous Membrane	Period of Observation Before Entry	Observed at Entry
Group A				
1	+	+	7 years	Atrophy of papillae
2	+	+	4 years	Atrophy of papillae
3	+	+	5 years	Atrophy of papillae
4	+	+	5 years	Atrophy of papillae, aphthae of mucous membrane
5	+	+	15 years	Aphthae of tongue, atrophy of papillae
6	+	+	2 years	Red, smooth tongue, aphthae, red mucosa
7	+	+	1 year	Red, smooth tongue
8	+	+	5 years	Red tongue, aphthae of mucosa
9	0	0		
10	+	+	7 years	Atrophy of papillae
Group B				
11	+	+	3½ years	Aphthae of mucosa
12	+	+	9 years	
13	+	+	1½ years	Atrophy of papillae, aphthae of mucous membranes
14	+	+	11 months	Red tongue
15	+	+	8 years	Aphthae of mucous membrane
16	+	+	1½ years	
17	+	+	4 months	Red, smooth tongue, aphthae of tongue and mucosa
18	+	+	6 years	Atrophy of papillae, aphthae of mucous membrane
19	+	+	6 months	Red tongue, atrophy of papillae
Group C				
20	0	0		
21	+	+	3 years	
22	0	+	10 years	Tongue red along edges
23	+	+	2 years	Tongue red along edges, atrophy of papillae
24	0	+	1 year	
25	+	0	13 years	Slight atrophy of papillae
26	+	+	4 years	Slight atrophy of papillae, tongue red at tip
27	0	+	1 year	Slight atrophy of papillae
28	+	+	7 years	
29	+	+	6 months	Aphthae of mucosa, tongue smooth
30	+	+	6 years	
31	0	+	3 years	
32	+	+	3 years	Redness and aphthae of tongue and mucous membrane
33	+	0		

one patient (case 7), in whom microcytic hypochromic anemia had been noted. A red blood cell count of less than 3,500,000 per cubic millimeter was arbitrarily selected as indicative of distinct anemia, since the frequent macrocytosis warranted the employment of erythrocyte counts rather than hemoglobin values as a criterion.

At the time of admission to the hospital all of these ten patients had red blood cell counts of less than 3,500,000, and the erythrocyte levels of two were below 1,000,000. The hemoglobin values were relatively high, giving all the patients, except in cases 6 and 9, a definitely

macrocytic hyperchromic blood picture. The color index and the mean corpuscular volume were well above the normal range and in many instances were at levels as high as those seen in pernicious anemia. In cases 6 and 9 the anemia was of a normocytic type.

As in pernicious anemia, the number of white blood cells was decreased, in six cases below 5,000. In only one was the count more than 6,000.

TABLE 4—*Gastric Analyses**

Case	Volume, Cc				Free Hydrochloric Acid			
	I	II	III	IV	I	II	III	IV
Group A								
1	17	15	15	28	0	0	0	17
3	30	20	15	25	0	0	20	79
4	35	20	12	19	0	4	10	13
5	25	21	12	16	0	0	0	7
6	20	30	15	30	0	0	0	0
7	16	42	8	24	0	0	0	25
8	38	62	18		0	0	24	11
9	40	25	15	30	0	0	0	36
10	86	35	30		6	62	122	
Group average	33.0	30.0	15.5	24.6	0.7	7.3	19.5	23.5
Group B								
12					20	36		96
13	12	11	9		0	6	8	
14	26	15	25		0	9	31	
15	12	20	24	13	0	0	0	0
16					11			22
18	15		22	13	0		10	16
19	30	35	30	20	14	67	91	99
Group average	19.0	20.3	22.0	15.3	6.4	23.6	28.0	46.6
Group C								
20	23	15	10	20	0	0	0	0
21	30	25	20	35	0	23	37	70
22	20	10	15	30	5	9	20	38
23	22	20	15		0	0	12	
24	10	12	15	30	0	8	14	31
25	30	75	25	40	0	30	50	97
26					0	?	58	
27	14	15	10	25	0	0	14	32
28	66	42	30		25	25	56	
29	40	9	15		6	27	30	
30	55	40	15	60	0	24	20	53
31	30	10	12	16	2	8	14	20
32	30	12	32	40	0	0	0	0
33	10	10	24	40	10	18	24	40
Group average	29.2	22.5	18.3	33.6	3.4	12.5	24.9	38.1
Series average	29.0	24.8	18.0	27.7	3.3	12.8	23.8	30.5

* I represents data for specimen taken during fasting, II, specimen taken twenty minutes after an alcohol test meal, III, specimen taken forty minutes after test meal, IV, specimen taken twenty minutes after injection of histamine. The volumes under specimen I do not always represent actual volumes during fasting, as some of the patients were allowed to sip water while swallowing the tube.

By comparing the red blood cell count at the time of the patient's discharge with that on entry, the effect of antispasmodic therapy on the hematopoietic system is evident. More detailed studies of the blood are shown in the two accompanying charts (figs 1 and 2, cases 4 and 5, respectively). In each of these patients a rise in the reticulocyte count occurred and was followed by a remission.

The two following abstracts of cases are given to illustrate the type of patient included in this group

CASE 4—B M, a 37 year old American woman, entered the hospital complaining of attacks of diarrhea for seven years. She had resided in Cuba for twelve years. Seven years before entering the hospital she began to have attacks

TABLE 5—Data on the Blood

Case	Anemia Observed Before Entry	Values at Entry					Values at Discharge				
		Erythrocytes,		Hemo	White	Mean	Erythrocytes, Millions per Cu Mm	Hemo globin, Per cent- age	White Blood Cells per Cu Mm	Mean Corpuscular Volume, Cu Microns	Color Index
		per	cent-	Blood	Corpuscular						
		Millions per Cu Mm	age	Cells per Cu Mm	Volume, Cu Microns						
1	1 yr	0.82	22	2,100	131	1.34	4.17	76	5,200	92	0.92
2	1 yr	1.13	30	3,250	115	1.33	3.45	78	6,750	102	1.12
3	+	0.90	30	1,400	121	1.67	3.67	77	3,800	101	1.05
4	5 yr	2.05	67	2,050	135	1.63	3.98	92	7,250	100	1.16
5	1½ yr	1.38	35	1,150	102	1.27	3.04	67	6,650	97	1.12
6	+	3.10	59	9,600	91	0.95	3.90	80	6,700	101	1.03
7	10 yr	3.30	70	5,100		1.06	4.90	94			0.96
8	5 yr	2.96	79	5,400	138	1.34	3.85	82	7,700	100	1.06
9	3 mo	3.15	53	4,650	78	0.84	3.47	62	5,300	79	0.90
10	0	3.12	81	5,500	118	1.30					
Group average		2.19	53	4,020	114	1.27	3.83	79	6,170	96.5	1.04
Group B											
11	4 yr	4.61	97	12,850	90	1.05	4.97	100	12,250	86	1.05
12	5 yr	3.59	92	5,150	113	1.28	4.68	94	7,950	90	1.01
13	2 yr	3.67	87	7,700	108	1.19					
14	11 mo	4.69	77	6,100	74	0.83	5.86	77	8,900	70	0.72
15	0	4.40	95		111	1.08					
16	6 mo	4.64	105	5,900	95	1.14	4.37	105	6,350	102	1.20
17	2 mo	3.52	58	7,150		0.83	3.87	59	9,900	75	0.77
18	5 yr	4.02	83	7,000	94	1.04					
19	0	4.47	86	8,300	91	0.98	4.54	94		102	1.04
Group average		4.18	87	7,520	97	1.05					
Group C											
20	0	4.42	99	4,100		1.12					
21	8 mo	3.57	97	4,150		1.36	4.06	94	5,250	108	1.17
22	10 yr	5.05	99	4,000	84	0.98	4.62	90	4,300	86	0.98
23	+	3.48	90	7,550	103	1.30	3.39	92	5,400	115	1.36
24	0	4.08	91	6,500	99	1.12	4.13	84	7,950	92	1.12
25	0	3.87	96	4,150	106	1.24					
26	3 mo	4.18	106	4,300	110	1.27					
27	0	3.94	100	2,450	72	1.27					
28	0	3.94	90	9,350		1.14					
29	0	4.57	96	7,400	89	1.05					
30	6 yr	3.72	89	6,350	101	1.20					
31	0	3.96	83	7,600	82	1.05					
32	3 yr	3.60	91	8,600	115	1.27	3.85	96	7,000	104	1.25
33	0	3.51	90	10,150	102	1.28	3.57	83	8,600		
Group average		3.99	94	6,190	97	1.19					

of diarrhea accompanied with nausea, vomiting and abdominal cramps. Two years after the onset of these attacks the patient moved to a temperate climate and was free from symptoms for six months. At the end of that time the diarrhea returned, with soreness of the tongue and mouth. Anemia of severe degree was present. Liver extract was given by mouth, the diarrhea ceased, and the red blood cell count rose to 4,000,000 per cubic millimeter. The patient was well for one year, then the diarrhea and soreness of the mouth recurred but were alleviated by the use of a diet of meat and eggs. The anemia was not relieved by this diet, and two transfusions were given. She was well until one year before admission to the

hospital, when the diarrhea recurred and the high protein diet afforded no relief. About two months before she entered the hospital weakness and pallor appeared and were not relieved by orally administered liver extract.

Physical Examination—The patient was fairly well nourished but was pale. The tip and dorsum of the tongue showed atrophy of the papillae. There was a small yellow ulcer on the mucosa of the upper lip. The abdomen was distended and tympanitic.

Laboratory Examination—Gastric analysis showed free hydrochloric acid in all specimens except the one taken during fasting. There were 2,000,000 erythrocytes per cubic millimeter, 66 per cent hemoglobin, a color index of 1.65 and a mean corpuscular volume of 135 cubic microns.

Course—During the first three days the patient had from ten to fifteen bowel movements a day. She was then given daily intramuscular injections of 10 cc

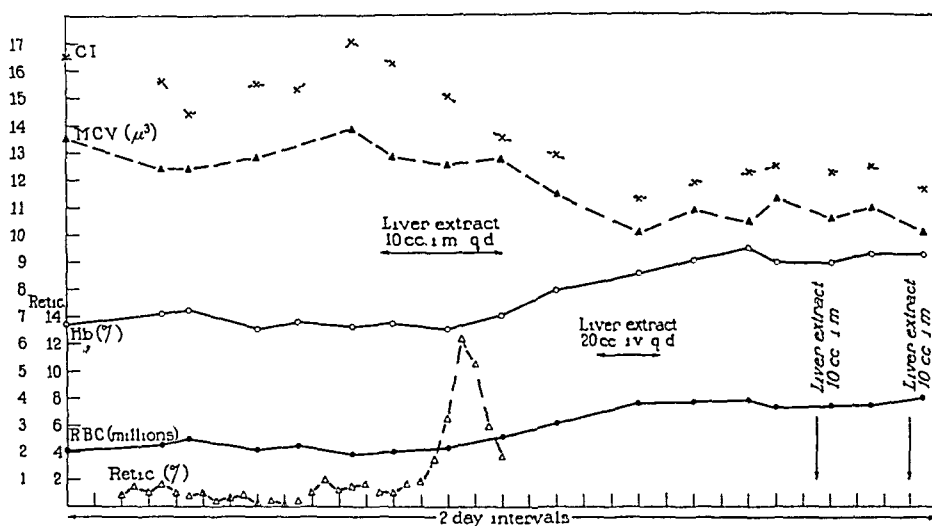


Fig 1 (case 4) —Chart of the changes in the blood following the parenteral administration of liver extract. In figures 1 and 2 the values for the color index (CI) have been multiplied by 10, the values for the mean corpuscular volume (MCV) in cubic microns have been divided by 10, the percentage values for hemoglobin (Hb) have been divided by 10, and the values for erythrocytes (RBC) have been divided by 1,000,000.

of liver extract,⁴ an amount derived from 50 Gm of whole liver. On the tenth day the reticulocyte count reached a peak of 12.8 per cent (fig 1). This was followed by an improvement in the blood values, and the patient was discharged from the hospital two months after entry, with an erythrocyte count of 3,980,000 and a hemoglobin value of 9.2 per cent. After discharge she received 10 cc of liver extract every two weeks by intramuscular injection, and on this regimen she was symptom free for nearly a year.

Nine months after discharge the patient went to Florida and discontinued the injections of liver extract. Two months later diarrhea recurred, and the patient lost her appetite and grew progressively weaker. From that time until her return to the hospital, five months later, attacks of diarrhea, soreness of the mouth and tongue, loss of weight and weakness became progressively worse. When readmitted she was having from fifteen to twenty evacuations daily.

4 Liver extract-Lilly (N N R) was used.

Physical Examination—The patient was emaciated. The tongue was red at the tip and along the margins. The buccal mucosa was injected, and there were several aphthous lesions. The abdomen was moderately distended, and peristaltic rushes were audible.

Laboratory Examinations—The results showed erythrocytes, 2,230,000, hemoglobin, 62 per cent, color index, 1.39, and mean corpuscular volume, 115 cubic microns.

Course—The patient was given 10 cc of liver extract by intramuscular injection daily for five days. Soreness of the tongue disappeared after the first injection, and the aphthous ulcers healed rapidly. Diarrhea ceased after the third injection. The number of injections of liver extract was decreased to two a week. In ten days the patient gained 2 Kg in weight. One month later the erythrocyte count was 3,350,000, and the hemoglobin value was 85 per cent. Injections of 10 cc of liver extract intramuscularly have been continued twice each week, and with this therapy the patient has remained essentially symptom free.

CASE 5—L. N., an American woman aged 45 who had resided in China for twenty-one years, had suffered from sprue for fifteen years. The presenting symptoms were stomatitis, glossitis, proctitis and diarrhea. Nine years before her entry into the hospital a remission had followed the use of a diet with a high protein, a low fat and a low carbohydrate content. For three years before her admission to the hospital nausea, vomiting and diarrhea, with marked loss of weight, had been present. For six months the patient had been in bed, able to retain only milk and toast. Twice a week during the three months immediately preceding her admission to the hospital she had received an intramuscular injection of 2 cc of liver extract, an amount derived from 10 Gm of whole liver.

Physical Examination—The patient was markedly emaciated. Pallor and faint yellowness of the skin and mucous membranes were noted. The tongue showed atrophy of the papillae. There was edema of the legs.

Laboratory Examination—The results showed erythrocytes, 1,380,000, hemoglobin, 35 per cent, white blood cells, 1,150, mean corpuscular volume, 102 cubic microns, color index, 1.27. Gastric analysis showed free hydrochloric acid only after the injection of histamine.

Course—The patient was given 20 cc of liver extract⁵ intravenously each day during her stay in the hospital. On the seventh day of treatment the reticulocyte value rose to 43.2 per cent. This reticulocyte response was followed by an increase in the erythrocyte count and in the hemoglobin value (fig 2). Diarrhea ceased soon after the injections of liver were begun. The patient's appetite improved, and she was discharged three weeks after entry, with an erythrocyte count of 3,040,000 and a hemoglobin value of 67 per cent.

After discharge from the hospital the patient moved to Alabama. She has received an intramuscular injection of 10 cc of liver extract every two weeks, and with this therapy she has remained free from symptoms for the past two and a half years.

Summary—These ten patients with severe sprue have been grouped together because of the fact that anemia as well as gastro-intestinal disturbance was present at the time of admission to the hospital. The histories of two patients in this group are presented. Case 4 demon-

⁵ Liver extract—Parke Davis & Co (N. N. R.) was used.

states the therapeutic failure of orally administered liver extract, as well as the necessity of continued therapy. Case 5 is presented because it is typical of severe spile and illustrates the dramatic results that can be obtained by intensive therapy with parenterally administered liver extract without change of diet.

Group B Patients With Diarrhea but Without Anemia—This group is made up of nine patients who had distention and diarrhea but no anemia at the time of admission to the hospital. The lack of disturbance of hematopoiesis separates these patients from those just described. Seven members of this group had resided in tropical or

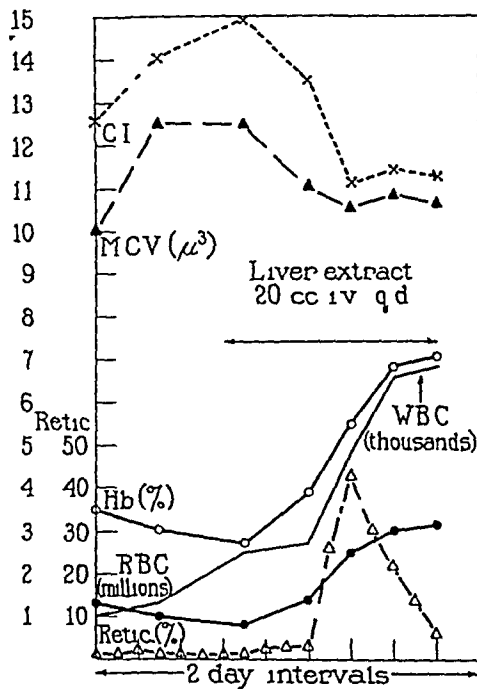


Fig 2 (case 5)—Chart of the changes in the blood following the parenteral administration of liver extract⁵

subtropical countries, whereas two had not been out of the temperate zone.

Gastro-Intestinal Symptoms (Table 1) Recurrent attacks of distention and diarrhea had occurred in every instance over periods varying from one to nine years. The gastro-intestinal symptoms did not differ from those of the patients in group A, except that nausea and vomiting had been less frequent and the attacks of diarrhea had not extended over so long a period.

At the time of admission to the hospital all these patients had diarrhea. The stools were on the whole not so numerous as those of the patients of group A but were of similar type.

Loss of Weight (Table 2) Six of the nine patients had lost weight over periods of from one month to nine years, but the average loss was not as great as in the preceding group, and the patients were not so emaciated. Since the period of hospitalization was relatively short, the gain in weight was correspondingly less striking in this group.

Oral Symptoms (Table 3) The oral symptoms of these patients were identical with those of the patients in group A. All of these patients had noticed soreness of the tongue or of the mouth over periods varying from four months to nine years. In most instances the oral symptoms first developed after the onset of the diarrheal attacks.

The same types of oral lesions were observed as have been described for the patients with more severe involvement. Two of these patients had no oral changes when they were admitted to the hospital, although they both gave a history of soreness of the mouth. Four patients had aphthous lesions of the oral mucosa, and two of these showed also atrophic glossitis. Three other patients were suffering from acute glossitis, with redness of the tongue, of these, one had atrophy of the papillae as well, and another had aphthous ulcers of the buccal mucosa.

Gastric Analysis (Table 4) Gastric analyses were carried out for seven patients of this group. In only one patient (case 15) was no free hydrochloric acid found in the gastric juice after the injection of histamine. The other six patients showed free hydrochloric acid either in the specimen taken during fasting or after the alcohol test meal. The quantities of gastric juice obtained were small.

Blood Picture (Table 5) Some of the nine patients gave a history of having suffered from anemia at some time during the course of their illness. However, at the time of admission to the hospital all the patients had red blood cell counts above 3,500,000. One patient (case 17) showed a hemoglobin value of 58 per cent, nevertheless, he is included in this group, since the erythrocytes numbered 3,520,000. Three of the patients had erythrocyte counts between 3,500,000 and 4,000,000, three had counts between 4,000,000 and 4,500,000, and three had counts between 4,500,000 and 5,000,000. In three instances the mean corpuscular volume and the color index were above the normal range, giving these three patients (cases 12, 13 and 15) a slightly macrocytic hyperchromic blood picture. In all the remaining cases the blood was normocytic.

CASE 12—R. B., a white man aged 56, had suffered from sprue for nine years before admission to the hospital. He had resided in Puerto Rico for five years when diarrhea first developed. This attack was characterized by large foamy stools and was accompanied with nausea and vomiting. Soon after the onset of the gastro-intestinal symptoms his tongue became sore, and salivation increased. During the next two years diarrhea, consisting of two or three spruelike stools, persisted, and the tongue was sore from time to time. Four years after the onset

of symptoms the patient returned to the United States. At that time he had lost about 15 pounds (7 Kg) in weight, diarrhea and soreness of the tongue and mouth were still present. The administration of liver by mouth was followed by striking improvement. When he discontinued liver therapy a year later, diarrhea again developed, and he began to lose weight. For fifteen months he was given daily intramuscular injections of 3 cc of liver extract⁴. On this regimen he felt well but finally tired of the injections and discontinued them. He was then given three vials of liver extract⁴ a day by mouth with the result that diarrhea and the loss of weight soon recurred, along with increasing fatigue. He was given 2 cc of liver extract by intravenous injection once a week, with no improvement in his symptoms. There was no response to a strict dietary regimen for sprue.

Physical Examination—The patient was well developed and fairly well nourished but appeared to be chronically ill. There were raised, rough, granular patches of skin over the elbows and knees. The tongue and mouth showed no abnormality.

Laboratory Examinations—Gastric analysis showed free hydrochloric acid in all specimens. Study of the blood showed erythrocytes, 3,590,000, hemoglobin, 92 per cent, leukocytes, 5,150, color index, 1.28, and mean corpuscular volume, 113 cubic microns.

Course in Hospital—The patient was given a diet for sprue and daily intravenous injections of 20 cc of liver extract (the amount derived from 50 Gm of whole liver). Dramatic relief from symptoms and complete amelioration of the gastro-intestinal disturbances resulted. The patient was discharged three and a half weeks after admission to the hospital, with instructions to take 20 cc of liver extract by intravenous injection once a week.

Subsequent Course—After leaving the hospital the patient received 20 cc of liver extract intravenously every ten days. After each injection the stools were formed for three days, semifformed for three days and loose and foamy for the last four days of the interval between injections. Marked flatulence accompanied the diarrhea, but no recurrence of the stomatitis or anemia developed. In spite of the gastro-intestinal disturbances the patient gained 6.2 Kg in the six months following his discharge from the hospital. He was then readmitted and treated with daily intravenous injections of 20 cc of liver extract for eleven days. On the third day of this course of therapy the stools became formed and remained so during the patient's stay in the hospital. He was again discharged as symptom free and received two intravenous injections of liver extract a week after that. On this regimen he has remained symptomatically well for nine months.

CASE 15—M. L. F., a 42 year old American woman who had resided for twelve years in southern China, had suffered from sprue for eleven years. The first attack of diarrhea occurred eleven years before her entry into the hospital and was not accompanied with fever, nausea or vomiting. Attacks of diarrhea recurred frequently during the next three years and were accompanied with soreness of the tongue and mouth. For the next five years the patient was symptom free. Three years before her entry into the hospital diarrhea with soreness of the tongue and mouth returned. After one year she was given a diet for sprue, consisting of liver, meat, fresh vegetables and fruits, on this diet she was symptom free for six months, after which her symptoms returned. For one year before her entry into the hospital the diarrhea was so severe that she was forced to give up her work and return to this country.

Physical Examination—The patient was fairly well nourished. The tongue showed no atrophy of the papillae, but there were numerous small yellow ulcerations of the buccal mucosa. The abdomen was moderately distended and tympanic. Peristalsis was audible.

Laboratory Examination—Gastric analysis showed no free hydrochloric acid, even after the injection of histamine. Study of the blood showed red blood cells, 4,400,000, hemoglobin, 95 per cent, white blood cells, 5,600, mean corpuscular volume, 111 cubic microns, and color index, 1.08.

Course—The patient was given a diet with a high protein, a low fat and a low carbohydrate content. Five cubic centimeters of liver extract was given intramuscularly daily for five days and then 20 cc by intravenous injection daily for eight days. With this therapy the diarrhea and flatulence ceased, and the oral lesions disappeared. The patient was discharged six weeks after entry.

After discharge the patient received intramuscular injections of 10 cc of liver extract twice a week for one month. The interval between injections was then lengthened, depending on how long the patient remained symptom free. Nine months after discharge from the hospital the patient returned to China. Since then she has received 10 cc of liver extract by intramuscular injection every two or three weeks and has remained entirely free from symptoms.

Summary This group consists of nine patients who had sprue with diarrhea but without anemia. Their complaints at the time of entry were chiefly of gastro-intestinal disorders. Two typical cases of this group are presented, both of which illustrate the amelioration of intestinal dysfunction which may be obtained by the parenteral injection of liver extract, although dietary therapy has been ineffective.

Group C Patients Without Anemia or Diarrhea—This group includes fourteen patients who had no diarrhea or anemia at the time of admission to the hospital. All had resided in tropical or subtropical countries, and all presented symptoms which warranted the diagnosis of sprue.

Gastro-Intestinal Symptoms (Table 1) Before entry into the hospital all these patients had had repeated attacks of flatulence and diarrhea over periods varying from one to twenty-five years. These attacks did not differ from those of the patients in the preceding groups. Five patients complained of nausea and vomiting as a frequent symptom. All the patients in the group had had voluminous, frothy, yellow, foul stools at one time. The ingestion of fatty or starchy foods had aggravated their symptoms.

On admission to the hospital these patients had no diarrhea. All except three of them had severe abdominal discomfort marked by abdominal cramps, audible peristalsis, rumbling of gas and frequent expulsion of gas both by mouth and by rectum. The stools were often soft or semiformal, but many had formed stools which were of normal appearance.

Loss of Weight (Table 2) Loss of weight had taken place in ten patients over periods varying from fourteen months to ten years. For the patients who had kept accurate figures for the amount of weight lost the values ranged from 4.6 to 18.2 Kg. At entry the patients were not so emaciated as those of group A or group B.

Oral Symptoms (Table 3) The oral symptoms of these patients were similar to those of the patients in the preceding groups. Before admission thirteen of the patients had suffered from soreness of the mouth at irregular intervals over periods varying from six months to thirteen years. In seven cases soreness of both the tongue and the oral mucosa had occurred, while two patients complained of soreness of the tongue alone and four patients of soreness limited to the oral mucous membranes.

At the time of admission to the hospital seven patients presented oral lesions. Five had atrophic glossitis, of these, two showed reddening of the tongue, and one had aphthous ulcers on the buccal mucosa. Two other patients had no papillary atrophy but did have redness of the tongue, one of them had aphthous lesions of both the tongue and the oral mucosa.

Gastric Analysis (Table 4) Gastric analyses were made for all the patients of this group. In two patients (cases 20 and 32) no free hydrochloric acid was found in the gastric juice even after the injection of histamine. In two patients (cases 23 and 27) free hydrochloric acid first appeared in the specimen taken forty minutes after the administration of the alcohol test meal. In most instances the volume of gastric juice and the content of free hydrochloric acid were approximately normal. The results of the gastric analyses for these patients approached the normal more closely than did those for the patients in the other two groups.

Blood Picture (Table 5) Anemia had occurred in six of these patients at periods varying from three months to ten years before entry, but at the time of admission to the hospital it was present in none. The red blood cell counts of eight patients were between 3,500,000 and 4,000,000, the other six had counts of over 4,000,000. The hemoglobin levels for seven of the patients were relatively high in proportion to the erythrocyte counts, and the values for the mean corpuscular volume and the color index were above the normal range. Thus, these seven patients showed a moderately macrocytic hyperchromic blood picture, even though they did not have anemia. In three cases the mean corpuscular volume was not determined, but the color index was high. The remaining four patients in the group had a normocytic type of blood picture.

CASE 29—M. P., a 57 year old American woman, was admitted to the hospital with complaints of soreness of the mouth and abdominal discomfort. For thirty-

two years prior to entry she had resided in Japan. She suffered her first attack of diarrhea, accompanied with nausea and vomiting, twelve years before admission to the hospital. She recovered from this episode and remained well until six years later, when abdominal discomfort, flatulence, diarrhea and soreness of the mouth developed. These symptoms persisted irregularly until one year before her entry into the hospital, when she had a severe attack of diarrhea. This symptom then disappeared, but the soreness of the mouth and flatulence persisted.

Physical Examination—The patient was well developed and well nourished. Two small yellow punched-out ulcers were present on the mucous membrane of the lower lip. The tongue showed atrophy of the papillae well up over the dorsum. The remainder of the examination revealed essentially normal results.

Laboratory Examinations—Gastric analysis revealed free hydrochloric acid in all specimens. Examination of the blood gave the following results: erythrocytes, 4,570,000, hemoglobin, 96 per cent, color index, 1.05, mean corpuscular volume, 89 cubic microns, and leukocytes, 7,400.

Course—The patient had no diarrhea on entry but had marked flatulence and abdominal discomfort. She was given a diet for sprue and intramuscular injections of 10 cc of liver extract daily for eight days. After this treatment the symptoms were markedly abated. The ulceration of the mouth disappeared, and the tongue was no longer sore. Abdominal discomfort, though still present, was much less marked at the time of the patient's discharge from the hospital. Thereafter she received two injections of liver extract a week for one month, then one injection a week for four weeks and finally one injection every two weeks. With this course of therapy she has become practically symptom free.

CASE 32—E. S., an American woman of 37 who had resided in Egypt and northern Africa for seven years, suffered her first attack of diarrhea six years before entry into the hospital. Five or six afebrile attacks characterized by from eight to ten loose to watery stools a day occurred during the first year of her illness. Two years later soreness of the tongue and mouth developed, diarrhea recurred frequently but was not so severe and the stools showed spruelike characteristics. Three years before entry liver extract was given by mouth, with improvement. One year later the patient was found to have microcytic anemia and was again given liver extract as well as iron by mouth. After this therapy the diarrhea ceased and had not recurred when the patient was seen in this clinic. At that time she complained chiefly of abdominal discomfort and flatulence. She was given a yeast autolysate⁶ for two months. At the end of this period stomatitis and glossitis developed. The abdominal discomfort was still present, and she was admitted to the hospital.

Physical Examination—The patient was well developed and well nourished. The only abnormalities noted were several aphthous ulcers on the buccal mucosa, with injection and redness of the entire oral mucous membrane. The tongue was red, raw and obviously sore.

Laboratory Examinations—Gastric analysis showed no free hydrochloric acid even after the injection of histamine. Studies of the blood showed erythrocytes, 3,600,000, hemoglobin, 91 per cent, color index, 1.27, and mean corpuscular volume, 115 cubic microns.

Course—The patient was given 10 cc of liver extract by intramuscular injection daily for four days. The glossitis, stomatitis and flatulence disappeared. Since discharge she has remained symptom free for ten months while taking a single intramuscular injection of 10 cc of liver extract once every two weeks.

⁶ The preparation used was *vege*x

Summary This group consists of fourteen patients who gave a history of repeated attacks of diarrhea. All except one had had soreness of the mouth. None of them had diarrhea on admission to the hospital, but eleven had symptoms referable to the gastro-intestinal tract. This is a group of patients with "incomplete sprue," that is, patients observed between attacks of the disease. Two typical cases are presented both

TABLE 6—*Roentgen Studies of Small Intestine*

Case	Variation in Caliber		Changes of Mucosal Pattern		Segmentation
	Jejunum	Ileum	Jejunum	Ileum	
Group A					
1	+	+	+	+	+
3		+	+	+	
4	+	+	+	+	-
5	+	+	+	+	-
6	+	+	+	+	+
7	+	+	+	+	+
8	+	+	+	+	-
9	+	+	+		-
10		+	+	+	+
Grand total (9 cases)	7	9	9	8	8
Group B					
11		+	+		-
12		+		+	+
13		+	+	+	
14	+	+	+	+	+
15	+	+	+		+
16		+		+	+
17					+
18		+			+
19		+		+	+
Grand total (9 cases)	2	8	5	5	8
Group C					
20	+	+	+		+
21		+	+		
23	+	+	+		+
25		+		+	
26	+	+	+	+	+
27		+		+	+
28		+		+	
29	+		+		
30		+		+	+
32		+		+	+
33		+			+
Grand total (11 cases)	4	10	5	5	7
Series total (29 cases)	13	27	19	18	23

of which demonstrate the effect of liver extract on the minor gastro-intestinal symptoms.

ROENTGENOGRAPHIC PICTURE (TABLE 6)

Morphologic alterations in the small intestines of patients with sprue, as demonstrated by roentgenograms, have been described in a previous paper.⁷

⁷ Mackie, T. T., Miller, D. K., and Rhoads, C. P. Sprue. Roentgenologic Changes in the Small Intestine, *Am J Trop Med* 15: 571, 1935.

Furthermore, a return toward normal form and function has been shown by roentgenographic means to accompany the cessation of symptoms following the injection of liver extract⁸ The chief morphologic alterations have been summarized as follows (1) a variation in the caliber of the intestinal segments, (2) a distortion of the mucosal pattern, usually of the jejunum but often of the duodenum and ileum as well, and (3) a segmental distribution of the barium, which is probably produced by abnormal motility of portions of the small intestine

Among these alterations the variation in the caliber of the intestinal loops and the distortion of the mucosal pattern are the most characteristic changes in sprue It is not assumed that these changes are pathognomonic of the disease, they are merely presented as observations which were made during the study of a large group of patients with sprue Snell and Camp⁹ have reported similar roentgenographic changes in cases of idiopathic steatorrhea Recently Ravdin, Pendergrass and their associates¹⁰ have studied the effect of various types of food on the roentgenographic pattern of the small intestine in normal persons As these authors pointed out, it is of interest that after an olive oil meal the intestine shows changes much like those seen in patients with various forms of steatorrhea Since poor fat absorption is a characteristic of sprue, it is possible that some of the changes observed in the pattern of the small intestine of patients with sprue are associated with the presence of an abnormal amount of fat in the bowel Few adequate roentgenographic studies of the small intestine in disease states have been carried out, it is therefore difficult to compare the findings in sprue with those present in other intestinal disorders

The method of roentgen examination used in this study was that previously described,¹¹ in the more recent studies the amount of barium sulfate used was reduced from 4 to 2 ounces (125 to 62 Gm) at the suggestion of Dr Golden, of the College of Physicians and Surgeons

8 Miller, D K, and Rhoads, C P The Effect of Liver Extract on the Small Intestine of Patients with Sprue, *Am J M Sc* **191** 453, 1936

9 Snell, A M, and Camp, J D Chronic Idiopathic Steatorrhea Roentgenologic Observations, *Arch Int Med* **53** 615 (April) 1934, *Proc Staff Meet, Mayo Clin* **10** 177, 1935

10 Ravdin, I S, Pendergrass, E P, Johnston, C G, and Hodes, P J The Effect of Foodstuffs on the Emptying of the Normal and Operated Stomach and the Small Intestinal Pattern, *Am J Roentgenol* **35** 306, 1936 Pendergrass, E P, Ravdin, I S, Johnston, C G, and Hodes, P J Studies of the Small Intestine II The Effect of Foods and Various Pathologic States on the Gastric Emptying and the Small Intestinal Pattern, *Radiology* **26** 651, 1936

11 Mackie, T T, and Pound, R E Changes in the Gastro-Intestinal Tract in Deficiency States, with Special Reference to the Small Intestine A Roentgenologic and Clinical Study of Forty Cases, *J A M A* **104** 613 (Feb 23) 1935

of Columbia University Table 6 summarizes the principal alterations which were seen in the roentgenograms of twenty-nine patients with sprue and illustrations from several cases are presented

Variation in Caliber of the Intestinal Loops—Variation in the caliber of the intestinal loops occurred most frequently in the ileum somewhat less frequently in the jejunum and rarely in the duodenum The greatest variations in caliber were noted in studies of patients with severe sprue Here the intestinal loops often appeared to be atonic, they were frequently dilated to such a degree that the diameter approached that of

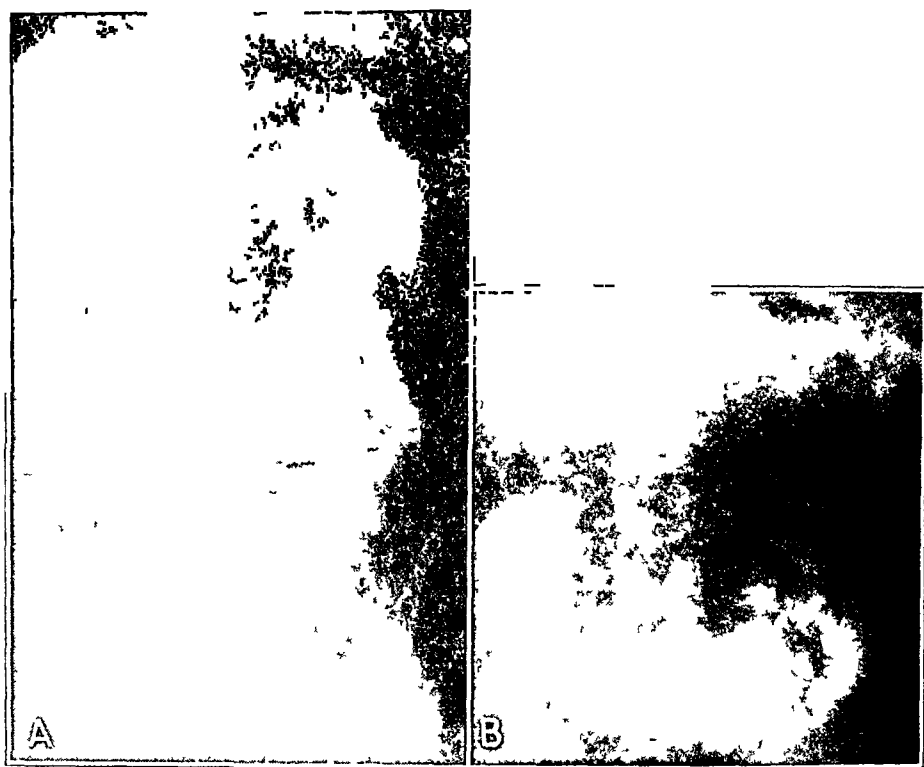


Fig 3—*A*, severe sprue (case 4) Note the abnormally dilated small intestine, with striking deviation of the mucosal pattern from normal *B*, mild sprue (case 29) Note the variation in the caliber of the intestinal loops

the large bowel (fig 3 *A*) In other instances the deviation from the normal caliber of the small intestine was less marked yet there was sufficient variation in caliber to suggest spasticity in certain areas and dilatation in others (figs 3 *B* and 5 *A*) In the severe form of the disease these changes were found in the jejunum and ileum, in the milder form the ileum alone was involved

Distortion of the Mucosal Pattern—Distortion of the mucosal pattern was commonly noted in the jejunum and ileum, less frequently in the duodenum The most striking changes occurred in the jejunum,

in the cases of milder involvement the delicate feathery pattern of the normal jejunum (fig 4 *A*) was replaced by a much coarser pattern (fig 4 *B*), whereas in many of the cases of more severe involvement the valvulae conniventes were markedly thickened and widely separated, giving rise to a picture not unlike that of the normal colon (fig 3 *A*)

All the patients of group A showed distortion of the mucosal pattern in the jejunum, and all but one showed similar alterations in the ileum. In groups B and C an equal number of patients showed changes in the jejunum and in the ileum.

Segmentation—Isolated segments of the intestine frequently presented a sausage-like appearance, which was usually observed in the middle and lower portions of the ileum (fig 5 *A*). This segmental

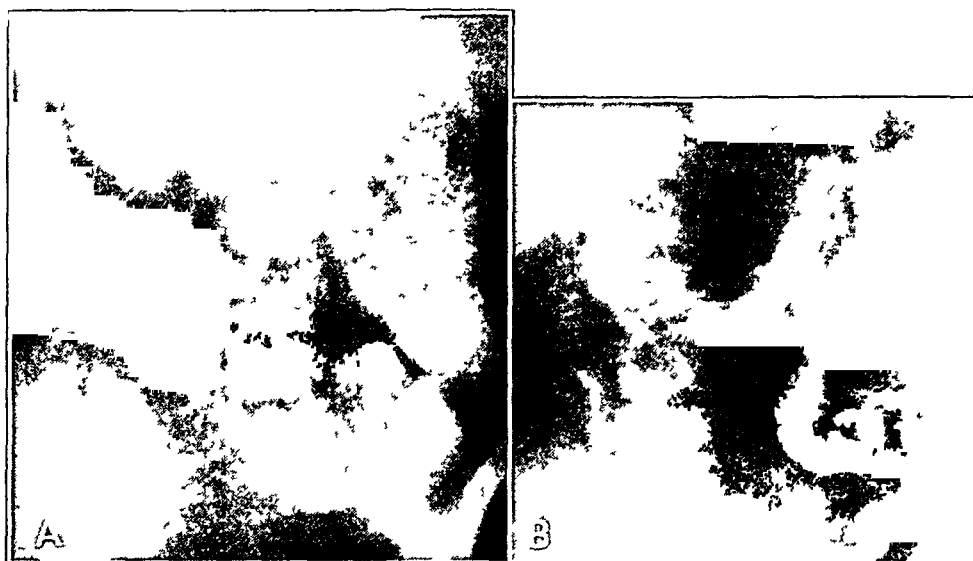


Fig 4—*A*, mild sprue (case 32). The essentially normal jejunum should be compared with the appearance in figures 3 *A* and *B* and 4 *B*. *B*, mild sprue (case 29). Note the distortion of the mucosal pattern of the jejunum.

distribution or pocketing of the barium was considered to be due to an irregularity of the movement of the contrast medium. The segmentation was interpreted as caused by alternating areas of spasticity and dilatation of the intestine. This type of segmentation was observed in all patients of groups A and B except one and in some patients of group C. Such a patchy distribution of barium has been observed in other conditions associated with diarrhea.¹²

In addition to the three most common alterations of the small intestine just described, certain other abnormalities were noted. In twelve

¹² Mills, R. W. X-Ray Evidence of Abdominal Small Intestinal States Embodying an Hypothesis of the Transmission of Gastro-Intestinal Tension, *Am J Roentgenol* 9:199, 1922.

instances the barium advanced through the small intestine in a divided column (fig 5 *B*), whereas normally the column is continuous. This separation of the opaque material into two or more columns suggested that the progression was temporarily arrested at one or more points along the intestinal tract. A terminal ileum which seemed to be straighter and more rigid than normal was observed in eleven cases. The roentgenographic picture of the colon was essentially normal in every instance in which a barium enema was given.

Summary of Roentgen Findings—A distortion of the mucosal pattern and a variation in the caliber of the intestinal loops were the most significant changes observed roentgenographically in the small intestines.

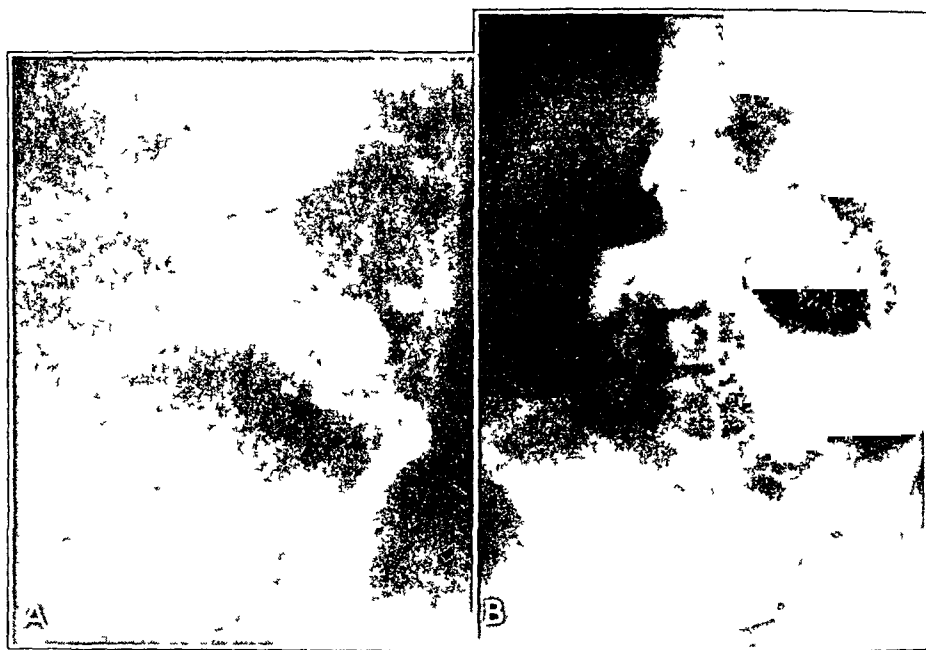


Fig 5—*A*, severe sprue (case 1). Note the variation in the caliber of the ileal loops and the segmental distribution of the barium in the ileum. *B*, note the separation of the barium meal into two columns (case 4).

in twenty-nine cases of sprue. All the patients showed these changes in various degrees. In general, the more severe the disease, the more pronounced the morphologic alterations. The roentgenographic findings should not be regarded as pathognomonic of sprue, as no comparisons can be made until more patients with other intestinal disorders have been studied by the same technic. Nevertheless, a correlation appears to exist between the severity of the disease and the extent of the morphologic alterations. Furthermore, these changes can be shown to regress after the use of specific antisprie therapy.

TREATMENT

The results obtainable through the adequate treatment of sprue are convincingly illustrated by this series of thirty-three patients. For the purpose of discussion the therapy employed is most conveniently divided into three phases: (1) treatment before admission to the hospital, (2) treatment during hospitalization and (3) treatment following discharge from the hospital.

1 *Treatment Before Admission to the Hospital* (Table 7) —It is of interest to review briefly the various types of treatment administered to the patients of this series before they were admitted to this hospital. Table 7 summarizes the treatment and results under three separate headings, diet, liver extract administered orally and liver extract administered parenterally.

Of the twenty-seven patients for whom a dietary regimen had been prescribed, twenty-two had been given some form of diet for sprue, that is a diet high in protein and low in carbohydrate and fat. Six received no benefit from this diet, whereas sixteen showed distinct improvement early in the course of the disease. Six of the sixteen patients who improved had been specifically instructed to include whole liver in their diet. Once the symptoms of sprue had been controlled by strict dietary measures, the patients took liberties with their diet or abandoned it entirely. The result was a recurrence of gastro-intestinal and oral symptoms. When such relapses set in, the patients frequently found that diets which had induced remissions in the past were no longer effective. Case 12, described in detail previously, well illustrates such a sequence of events.

Seven patients had received liver extract orally at one time or another during the course of their illness. Four were temporarily improved, whereas three were unimproved.

Liver extract had been administered parenterally to twelve patients. Three showed distinct symptomatic relief. Six were temporarily benefited and, to judge from the subsequent course, would have continued to improve if the parenteral therapy had been continued. In three cases the symptoms were not alleviated, presumably because the amount of liver extract given was too small. For example, one patient (case 12) did well when he received an intramuscular injection of 3 cc of liver extract every day, yet later he showed no response to an intravenous injection of 2 cc once a week.

It is apparent that the great majority of the patients in this series had been inadequately treated before they were admitted to the hospital. Temporary remissions had been effected in many cases both by dietary measures and by liver extract, but therapy had not been sufficiently intensive to maintain the patients in good health.

TABLE 7—Treatment Before Hospitalization*

Case	Diet	Result	Liver Extract, Oral	Result	Liver Extract Parenteral	Result		
Group A								
1	Cooked liver and sour milk (S)	Temp	3 vials q d , 14 months	No imp	2 cc intramusc q d , 5 weeks	No imp		
2	Eggs, milk and chopped meat, no starch or carbohydrate (S)	No imp						
3	Rice and few vegetables	No imp	6 vials q d , 3 months 9 vials q d , 6 months	Temp	2 cc intramusc twice a week	No imp		
4	Meat and eggs (S)	Temp						
5	High protein, low carbohydrate and fat (S)	Temp	Exact amount not known	No imp	Intraven injections for 3 weeks	Temp		
6	Cereals, eggs, milk, fruit juices, bananas, cream, high protein and cooked liver (S)	Temp						
7	a Low residue b High protein (S)	Temp No imp						
8					10 intramusc injections, 4 weekly for short time	Temp		
9	High protein (S)	No imp	Group B					
10	a Eggs, milk and bananas (S) b Brown bread and pineapple	Temp Worse						
11	Coffee, cereal, bread, pork, chicken and some milk	No imp						
12	Diet for sprue with liver (S)	Temp			a 3 cc intramusc q d , 5 months b 2 cc intraven weekly	Imp , tired of treatment No imp		
13	Low starch (S)	Temp						
14	a High protein, low fat and carbohydrate (S) b Raw meat and bananas (S) c High carbohydrate, little fat or protein	No imp						
15	a Liver, meat and fish (S) b Fish, fruit, vegetables, potatoes, broths, custards and crackers	Temp Temp						
16	(S)	Temp			10 cc intramusc twice a week	Imp		
17	Low residue	Slight, temp	Group C					
18	a 3 qts of milk, grape fruit juice, rare beef and liver added (S) b Liver with milk and red meats (S)	Temp						
19	Eliminated orange juice	Temp						
20	Eliminated fatty and starchy foods (S)	Temp						
21					a 10 cc intramusc q week b 2 cc intramusc twice a week	Temp Temp		
22	(S)	No imp			Small amount irregularly	Temp		
23	a Skimmed milk and strawberries b Fruits and vegetables with red meat (S)	No imp Temp			4 capsules q d , 6 months	Temp	39 cc intramusc in 2 weeks	Temp
24	(S)	No imp						
25	Rare scraped beef and Bulgarian buttermilk (S)	Temp						
26	Fresh vegetables and meat (S)	Temp						
27	High protein (S)	Temp	3 vials q d , 3 months	Temp				
28								
29								
30	High meat diet with liver (S)	Temp					2 courses of treatment	Temp
31	Low fat low salt diet	No imp						
32								
33								

* (S) signifies diet for sprue temp, temporary improvement imp, improvement, no imp, no improvement, intramusc, intramuscularly, and intraven, intravenously

2 *Treatment During Hospitalization* (Table 8) —The three chief therapeutic measures employed in the treatment of these patients in the hospital were (a) rest in bed, (b) a diet for sprue and (c) liver extract given parenterally

(a) *Rest in Bed* Complete rest in bed was of course essential in the cases of severe sprue and also furnished a useful adjunct to the more specific forms of therapy in the cases of a milder degree of involvement. It was not uncommon to find that a patient required more intensive therapy when ambulatory than when at rest in bed. Undue fatigue appeared to play a prominent rôle in the precipitation of relapses.

(b) *Diet for Sprue* The diet for sprue as used in this clinic was essentially high in protein and low in carbohydrate and fat. Emphasis was placed on the taking of large amounts of rare red meat. The dietary regimen is presented in table 9. Practically all the patients received this diet unless the severity of their condition made such a measure impossible. Then the patient was given nothing but ground meat and milk until he could partake of a more liberal fare.

Three patients in group C were treated with the diet for sprue alone and became practically symptom free on this regimen. One patient was not treated, as he was referred to this hospital for diagnostic study only. For the remaining twenty-nine patients the dietary treatment was not effective until it was supplemented with injections of liver extract. No patient with sprue of moderate or severe degree was seen for whom dietary treatment alone brought about complete amelioration of symptoms.

(c) *Liver Extract* Unless otherwise specified, solution of liver extract for parenteral use, both intramuscular and intravenous, was prepared from liver extract⁴ which met the standard given in "New and Nonofficial Remedies." The concentration of the solution for intramuscular injection was twice that of the solution for intravenous use. The solutions were made up so that 10 cc. of the intramuscular preparation or 20 cc. of the intravenous preparation contained the amount of extract derived from 50 Gm. of whole liver. The maximal and usual dose of the intramuscular extract given at one time was 10 cc., of the intravenous extract, 20 cc. An intramuscular injection was sometimes productive of soreness and burning at the site of injection but was rarely followed by systemic reactions. The intravenous injections were occasionally followed by chills, fever, flushing, headache, nausea or urticaria. No reactions so severe as to require cessation of treatment were observed.

The total amount of liver extract injected into a given person during the period of hospitalization depended on the severity of the symptoms, the grade of anemia and the rapidity of the response to therapy. All the

TABLE 8—Treatment

Case	During Hospitalization				After Discharge		Total Period of Observation
	Diet	Liver Extract, Intra muscular	Liver Extract, Intra venous	Result	Liver Extract	Comments	
Group A							
1	No bread or potatoes	20 cc 1 day 10 cc q d , 9 days 2 cc q d , 6 days 10 cc q d , 9 days		Improve ment Diarrhea	10 cc q 2 weeks	Well	4½ yr
2	Sprue	10 cc q d , 3 days 10 cc q 2 weeks 10 cc q 10 days		Improve ment	20 cc q month	Returned to Puerto Rico, symptom free	4½ yr
3	Sprue		20 cc q d , 30 days	Improve ment	10 cc q 2 weeks	Well	3½ yr
4	Sprue	10 cc q d , 10 days	20 cc q d , 5 days	Improve ment	10 cc q week 10 cc twice a week	Discontinued liver, had relapse in 2 months, readmitted, now symptom free	3½ yr
5	Sprue	10 cc q d , 4 days	20 cc q d , 10 days	Improve ment	10 cc q 2 weeks	Symptom free	3 yr
6	Sprue	10 cc q d , 30 days	20 cc q d , 20 days	Improve ment tem porarily		Died of tuberculous peritonitis	6 mo
7	Sprue		20 cc q d , 5 days	Improve ment	Irregular	Died of carcinoma of pancreas	1¾ yr
8	Light	10 cc q d , 10 days		Improve ment	10 cc q 2 weeks	Relief of symptoms	4 yr
9	Sprue		20 cc q d , 13 days	Improve ment		Discharged against advice, not followed	2 mo
10	Sprue	10 cc q 2 days for 10 injections		Improve ment	10 cc q week	Symptom free	1 yr
Group B							
11	Sprue	10 cc q d , 10 days		Improve ment	10 cc q week	Well	1¼ yr
12	Sprue		20 cc q d , 8 days	Improve ment	20 cc in traven ously q 7-10 days, twice weekly	Fairly well at first symptom free on treatments twice weekly	2¼ yr
13	Sprue	10 cc q d , 7 days		Improve ment	10 cc twice weekly	Not improved	2¼ yr
14	Sprue		20 cc q d , 11 days	Improve ment	10 cc q 10 days	Well	2¼ yr
15	Sprue	5 cc q d , 5 days	20 cc q d , 8 days	Improve ment	10 cc q 2 weeks	Returned to China, well	3¼ yr
16	Sprue		20 cc q d , 5 days	Improve ment	10 cc q week	Well	2½ yr
17	Sprue	10 cc q d , 8 days	20 cc q d , 10 days	Improve ment		Not followed in clinic	4 mo
18	Sprue	10 cc q d , 7 days		Improve ment	10 cc q 2 weeks	Returned to Puerto Rico, well	2¼ yr
19	Sprue		20 cc q d , 20 days	Improve ment		Died of sprue in another hospital without therapy	1 yr

TABLE 8—*Treatment—Continued*

Case	During Hospitalization				After Discharge		Total Period of Observation
	Diet	Liver Extract, Intra muscular	Liver Extract, Intra venous	Result	Liver Extract	Comments	
Group C							
20	Sprue					Not treated in hospital	2 mo
21	Sprue	3 cc * q d , 13 days		Improve ment	10 cc q 2 weeks	Returned to Puerto Rico, well	1 yr
22	Sprue	10 cc q week		Improve ment	10 cc q week	Well	2 yr
23	Sprue	10 cc q d , 5 days		Improve ment	10 cc twice weekly, 10 cc q week	Well	2½ yr
24	Sprue	10 cc q d , 6 days 10 cc thrice weekly, 3 weeks	20 cc q d , 5 days	Improve ment	10 cc q 2 weeks	Well, returned to China	1¼ yr
25	Sprue	10 cc for 4 injections		Improve ment	10 cc q 2 weeks	Well	9 mo
26	Light	10 cc for 2 injections		Improve		Advised to return to China, not followed	1 mo
27	Sprue			Improve ment		Well on diet	1 yr
28	Sprue			Improve ment		Well on diet	3 mo
29	Sprue	10 cc q d , 8 days		Improve ment	10 cc q 2 weeks	Well	1 yr
30	Sprue	10 cc q week		Improve ment	10 cc q week	Well	1 yr
31	Sprue	10 cc q 2 days, 12 in jections		Improve ment	10 cc q 2 weeks	Well	1½ yr
32	Sprue	10 cc q d , 4 days		Improve ment	10 cc q 2 weeks	Well	1½ yr
33	Sprue			Improve ment		Fairly well on diet alone	6 mo

* Liver extract Lederle (N N R) was used

patients in groups A and B and ten patients in group C received parenteral injections of liver extract during their stay in the hospital. The amount of liver extract given to patients of groups A and B was greater than that given to patients of group C, as the former had a more severe form of the disease. One patient (case 6) received daily injections for fifty days with only temporary relief of his symptoms, this patient died later of tuberculous peritonitis. Another patient (case 3) received daily intravenous injections for thirty days. The majority of patients in the first two groups required daily injections over periods of from five to twenty days, whereas shorter courses of parenteral therapy usually brought about complete relief of symptoms in the patients in group C. The importance of intensive liver extract therapy in the treatment of

cases of severe sprue has already been emphasized¹³ Too much stress cannot be laid on the fact that much larger amounts of liver extract are generally necessary to control the symptoms of sprue than are required to induce a remission in a case of severe pernicious anemia

The alleviation of the various symptoms of sprue with combined dietary and liver extract therapy was on the whole phenomenal The

TABLE 9—*Diet for Sprue*

Breakfast	
Toast, 1 thin slice with a small piece of butter	
Fresh fruit, large serving	
Eggs, 2, prepared in any manner desired	
Milk, at least 1 large glass (this may be heated and used in place of cream for coffee or may be made into cocoa)	
Luncheon	
Meat, large serving ($\frac{3}{4}$ pound at least)	
Vegetables, 2, or 1 vegetable and salad	
Milk puddings, gelatin, ice cream or fresh fruit	
Crackers (2 only) with cheese	
Milk, 1 glass	
Dinner	
Fruit cocktail or tomato juice	
Beef broth or any cream soup (make cream soups with milk instead of cream and omit butter)	
Meat, large serving ($\frac{3}{4}$ pound at least)	
Vegetables, 2 at least	
Desserts, as for lunch	
Milk, 1 glass	
Egg nogs, milk or fresh fruit may be eaten between meals	
The diet should consist largely of protein	
Meat	Meat should always be lean and rare
	Beef, lean, either roast or steak
	Lamb, lean, either roast or chops
	Ham, lean
	Liver, tongue, heart, kidney or sweetbreads
	Fish, any fresh fish
	Chicken
	Lobster, crab or oysters
Milk and milk products	milk, buttermilk and American and cottage cheese
Eggs	prepared in any manner desired
All fatty foods should be avoided butter, cream, lard, olive oil and all oil salad dressing, avocado pears, pie, pastry and all foods fried in fat	
All starchy foods should be avoided potatoes, beans, corn, bread, cereals, cake and candy	

gastro-intestinal symptoms—diarrhea, flatulence, anorexia and nausea—cleared up entirely in all but two patients treated in the hospital When these symptoms were under control, the patients began to gain weight at a rate which was often astounding in view of the dietary restriction of carbohydrate and fat Soreness of the tongue and mouth disappeared, aphthous lesions healed and in those patients who showed papillary atrophy regeneration of the papillae took place

¹³ Rhoads, C P, and Miller, D K Intensive Liver Extract Therapy of Sprue, J A M A **103** 387 (Aug 11) 1934

No less striking was the improvement in the blood picture of those patients who had anemia. The red blood cell count, hemoglobin value and white blood cell count all returned toward normal levels, as did the mean corpuscular volume and the color index.

Thus it is apparent that the various clinical manifestations of sprue, both mild and severe, were dramatically alleviated in the great majority of cases by the institution of adequate therapy. In the cases of more severe involvement therapy was necessarily intensive at first, whereas in the cases of milder involvement several injections of liver extract, or at times dietary measures alone, sufficed to render the patients symptom free.

(d) *Adjunctive Therapeutic Measures* In addition to rest in bed, a diet for sprue and liver extract, certain other therapeutic measures were indicated in a small percentage of patients. These measures were blood transfusion, calcium salts and iron. If the anemia is so severe as to jeopardize the patient's life, blood transfusion should be given. Only one patient in this series (case 2) required transfusion. Calcium salts should be administered both orally and parenterally to patients with tetany, muscle cramps or osteoporosis. Two patients (cases 6 and 7) who had tetany were given intravenous injections of calcium chloride during the acute stage, later they were given calcium gluconate by intramuscular injection. Muscle cramps were relieved by the oral administration of calcium chloride in case 4. The addition of intramuscular injections of calcium to liver extract therapy afforded more complete relief from gastro-intestinal symptoms in a few cases. Occasionally the anemia of sprue was microcytic, or the blood picture changed from a macrocytic to a microcytic type after treatment with liver extract. In such cases iron, in the form of ferrous sulfate or iron and ammonium citrates, was given as a supplement to liver extract therapy.

3 *Treatment Following Discharge from the Hospital* (Table 8) — Perhaps more important than the alleviation of the acute symptoms is the maintenance of patients with sprue in good health over a prolonged period. Data are available for twenty-nine of the thirty-three patients over periods of from three months to four and one-half years after discharge.

Three patients of this series have died. One patient (case 6) died of tuberculous peritonitis after six months, and another (case 7) died of carcinoma of the pancreas after twenty-one months. It is of interest that the symptoms of both patients were temporarily relieved by anti-sprue therapy. One patient (case 19) died of sprue in another hospital, where he was not given specific therapy.

One patient (case 13) continued to have attacks of diarrhea, cramps and flatulence in spite of diet for sprue and injections of liver extract.

twice a week. The addition of liver extract orally and injections of calcium gluconate alleviated the symptoms to a certain extent but failed to afford complete relief. For this reason the patient was readmitted to the hospital for further study. No amebas were found in the stools, and culture revealed no pathogenic organisms. With rest in bed in addition to dietary and liver extract therapy, the diarrhea and cramps ceased, only to recur when the patient resumed her secretarial work. This is the only patient with tropical sprue whose symptoms have not been controlled by the antisprue regimen which has been described.

Another patient (case 33) has been only "fairly well" on the diet for sprue alone. To judge from the course of the other patients studied it is possible that an occasional injection of liver extract would render this patient free from symptoms.

The remaining twenty-four of the twenty-nine patients for whom adequate follow-up data are available have remained practically symptom free with continued antisprue therapy. Five of these patients have returned to tropical countries without a recurrence of symptoms. Two of the twenty-four have remained essentially well on the diet for sprue alone. The other twenty-two patients have required injections of liver extract at regular intervals. One patient is given an intravenous injection of 20 cc twice a week and another an intramuscular injection of 10 cc twice a week. Seven patients receive a single intramuscular injection of 10 cc once a week, twelve patients receive an intramuscular injection of 10 cc every two weeks and one patient remains symptomatically well with one intramuscular injection a month.

The interval that is allowed to elapse between injections of liver extract must be ascertained for each patient. Injections should be given at sufficiently frequent intervals to prevent the recurrence of gastro-intestinal symptoms. One patient (case 1) who has been followed for four years may be taken as an illustration of this principle. During the first year after discharge from the hospital this patient suffered from recurrent gastro-intestinal symptoms which began about ten days after an injection of liver extract, therefore she was treated once a week. More recently she has found that she remains free from symptoms for nearly three weeks after an injection, accordingly the inter-injection interval has been increased to two weeks.

The intimate relationship that exists between the injection of liver extract and the cessation of gastro-intestinal symptoms has been recognized by many patients. A patient who has symptoms as a result of transgressing the safe interval between treatments usually experiences complete relief from these symptoms within twenty-four hours after an injection of liver extract. Furthermore, a number of patients have found through repeated trials that soon after a treatment with liver

extract they may take many liberties with their diet with impunity, whereas during the latter part of the interinjection interval they must adhere strictly to the diet for sprue in order to prevent the recurrence of gastro-intestinal symptoms

Both mental and physical fatigue were often responsible for the onset of symptoms in these patients. During periods of stress the frequency of injections had to be increased. Case 30 serves to illustrate just such a situation. This patient suffered from a "nervous breakdown" several weeks after she had been rendered free from symptoms of sprue by specific therapy. During a period of two weeks she was upset mentally, ate little and received no liver extract. At the end of this period she had a typical relapse of sprue with diarrhea, flatulence and a sore red tongue. These symptoms cleared up rapidly when treatment with liver extract was resumed.

The question naturally arises as to whether the patient with sprue can ever abandon specific therapy entirely without suffering a relapse. All that can be said in answer to this question is that those patients who have voluntarily discontinued therapy have suffered relapses, this occurred, for example, in case 4, described in detail under group A. The majority of these patients have been unwilling to abandon their therapeutic regimen for fear of suffering a relapse. It is evident that the well-being of a patient with sprue is dependent on the regulation and maintenance of this specific regimen. The amount of liver extract which is necessary to prevent the recurrence of gastro-intestinal symptoms is far greater than that which is required to maintain normal blood values. Hence the basic principle in the treatment of sprue is the administration of an adequate amount of liver extract at sufficiently frequent intervals to prevent the recurrence of abdominal discomfort, flatulence and diarrhea.

SUMMARY AND CONCLUSIONS

A series of thirty-three patients with sprue has been studied. Twenty-nine of these patients have been followed in the clinic after discharge from the hospital. The patients have been divided into three groups on the basis of certain symptoms and clinical findings at the time of entry into the hospital. Ten patients presented the classic picture of severe sprue with diarrhea and anemia. Nine patients had diarrhea but no anemia, while the remaining fourteen complained only of abdominal discomfort and flatulence. The symptomatology, the blood findings and the results of gastric analyses for these patients have been presented in detail, together with abstracts of illustrative cases.

Roentgen study of the small intestine was made for twenty-nine of these patients, and morphologic alterations of the small intestine were observed in all, these changes varying directly with the severity of

the disease. The most significant abnormalities were a distortion of the mucosal pattern and a variation in the caliber of the intestinal loops. These roentgenographic changes are not regarded as being pathognomonic of sprue, since not enough studies of the small intestine have been made in cases of other gastro-intestinal disorders for purposes of comparison.

Treatment before, during and after hospitalization has been discussed in detail. The great majority of the patients experienced complete symptomatic relief once adequate therapy had been instituted. Moreover, these patients have been maintained in excellent health over long periods by means of a relatively simple therapeutic regimen. Five patients have returned to tropical countries without recurrence of symptoms. It must be emphasized that no patient has discontinued specific therapy entirely without suffering a relapse. The maintenance of a diet for sprue in addition to liver extract therapy gives a patient more complete relief of gastro-intestinal symptoms than does liver extract given parenterally alone. The frequency of injections of liver extract must be worked out for each patient, the prevention of intestinal dysfunction serving as a guide to the amount of therapy to be given.

ACUTE BISMUTH POISONING, WITH RECOVERY

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Bismuth toxemia, fortunately, is now rare. Five years ago one of us (A E O) prepared an alkaline solution of bismuth and potassium tartrate¹ for use as a cystographic medium and found it iocytogenologically satisfactory in more than one hundred cases and without toxic effect.² Subsequently, after the use of this substance prepared elsewhere, we observed two patients with acute bismuth toxemia, and we are reporting these cases because the symptoms and course were unusual.

The chief initial symptom was oliguria or anuria, and it was not until characteristic stomatitis developed later that bismuth toxemia was suspected. Experimental studies on animals have demonstrated that toxic amounts of bismuth salts will cause a disturbance in renal function,³ including azotemia and a renal lesion most noticeable in the tubular cells.⁴ A fatal case in which there was anuria with marked retention of urea in the blood was reported by Aubertin and Destouches⁵ in 1927. Dowds in 1936 made a report of three fatal cases with necropsies.^{5a} Early recognition of the condition and immediate institution of adequate therapeutic measures are therefore important to insure renal recovery.

From the Division of Medicine and the Section on Biochemistry, the Mayo Clinic

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REPORT OF CASES

CASE 1—The patient, a man aged 63, a foreman in a railroad roundhouse, was admitted to the clinic on July 12, 1932. In 1917 he began to have urinary frequency and urgency, which continued for one year, chills and fever due to a urethral abscess then developed which finally required perineal drainage. Intermittent recurring chills and fever followed, with recurrence of the abscess in the perineum. About 1928 the patient began having "bladder treatments," and he became practically free from symptoms for one and a half years prior to his admission to the clinic. The last cystoscopic examination was made five months previous to entry.

On physical examination at the clinic he weighed 213 pounds (96.8 Kg). A perineal scar was present, as was also a moderate degree of prostatic hypertrophy. The blood pressure in millimeters of mercury was 140 systolic and 90 diastolic. The value for hemoglobin was 16.7 Gm per hundred cubic centimeters, and the erythrocytes numbered 4,760,000 and the leukocytes 7,500 per cubic millimeter of blood. The serologic test for syphilis gave a negative result. There was a 55 per cent excretion of phenolsulfonphthalein in two hours. A roentgenogram of the kidneys indicated that the size and outline were normal. Urinalysis showed the specific gravity of the urine to be 1.027, it contained albumin (grade 1), no sugar and 50 pus cells per microscopic field.

On the first day (July 14) 150 cc of the bismuth solution was injected into the bladder and left there for from five to ten minutes while the cystogram was taken, it was then expelled as completely as possible. The cystogram revealed a normal vesical outline. A diagnosis was made of bilateral, median, intra-urethral prostatic hypertrophy, moderate prostatic fulness, chronic cicatricial urethritis and chronic bilateral pyelonephritis. There was no residual urine or any symptoms of discomfort. It seemed probable that the previous abscess was of prostatic origin. Toward evening of this day the patient noticed that the volume of urine was gradually decreasing. The last specimen was voided at 2 a. m. on July 15. He was then sent to the hospital, and treatment for oliguria was commenced. The next day, July 16, the output of urine amounted to only 20 cc, and the patient vomited 500 cc of fluid.

Between July 15 and August 7 the temperature ranged from 98 to 100.8 F and the pulse rate from 70 to 120 beats per minute. Vomiting continued for a period of eleven days (July 16 to 27). During this period the blood pressure ranged from 125 to 170 systolic and 60 to 90 diastolic. The ocular fundi were normal. Fluid given intravenously from July 15 to August 10 consisted of solutions containing 10 per cent dextrose, 1 per cent sodium chloride and 5 per cent sodium bicarbonate (table 1).

On July 17, the fourth day after the patient's admission to the hospital, an emergency cystoscopic examination was carried out, spinal anesthesia being employed. No urine was observed flowing from the left ureter, however, a few drops were seen coming from the right ureter. The patient had vomited a total of 1,150 cc of fluid in the past two days. On July 18 slight edema of the lower part of the legs was noticed. The patient was drowsy, oliguria and almost complete anuria had persisted for four days. Dr. Cabot carried out bilateral (simultaneous) renal decapsulation with the patient under spinal anesthesia. Both kidneys were enlarged, firm and rather granular, suggesting chronic nephritis (for chemical studies of the blood see table 1).

On the eighth day after entry (July 21) the patient was irrational at times, the blood pressure was 140 systolic and 70 diastolic. On the next day there was

TABLE 1—The Data for the First Patient

Day of Observa- tion	Intake of Fluid				Total Intake of Fluid, Cc	Urine†				Blood						Comment	
	Intravenous		Total, Cc			Volume, Cc	Protein, Grade	Casts, Grade	Erythrocytes, Grade	Leukoocytes, Grade	Hemoglobin, Gm per 100 Cc	Drythrocytes, Millions per Cu Mm	Urea, Mlg per 100 Cc	Creatinine, Mlg per 100 Cc	Serum Sulfate, Mlg per 100 Cc		Plasma Chlo- ride, Mlg per 100 Cc ‡
1							1				16.7	4.76					Phthalein excretion, 53 per cent
2		18.0		2,000	3,400	0											Cystogram normal vesical outline
3		29.0	200	3,000	5,075	20						90	4.3				Emesis, 500 cc
4		13.5		1,500	3,305	125						100	7.8				Emesis, 600 cc
5		13.5	150	1,500	3,850	68						124	9.3				Bilateral renal decapsulation, emesis, 550 cc
6		13.5	250	2,500	3,150	50				13.3	3.77	132	11.2				Bleeding from gums
7	25	0.9	60	900	2,180	5+	2	0	3			151	11.6		511	32	
8		27.2	200	2,800	3,330	9						200	12.0		728	43	Salyrgan, 0.5 cc
9	25	23.5	100	3,000	4,700	80				13.1	3.65	208	12.1		495	47	Salyrgan, 0.5 cc
10		5.0	150	1,500	2,250	400											Stomatitis, twitch- ing of muscles
11		1.5	250	3,000	4,060	850+											Colon bacilli in urine
12		15.4	250	3,100	3,500	2,000+	2	0	1			180	14.0		162	11	
13		15.0	300	3,000	4,000	1,900+				11.4	2.80	234	13.2		479	35	
14		14.5	270	3,000	4,000	2,400						231	13.2		479	33	
23		14.1		1,600	5,200	4,640						105	6.0	87	594	37	
30					3,000	2,700	0	0	0	17.4	4.37	40		7.1	619	51	
3½ years later												26		5.5			Urea clearance, 53 cc; sulfate clear- ance, 10 cc

* Data obtained on entry

† Variation of the specific gravity during toxæmia, 1.004 to 1.008

‡ Calculated as sodium chloride

considerable drainage of fluids (500 cc ?) through the wounds in the loin. On the eleventh day some twitching of the facial muscles and also ulcerative stomatitis and swelling of the tongue were noted. A diagnosis of possible bismuth poisoning was made. On the twelfth day cultures of the urine revealed colon bacilli. The blood pressure was 130 systolic and 65 diastolic on July 31. In the last week of July the patient's condition steadily improved. During the phase of acute oliguria, edema was never marked and was limited to the dependent parts of the back and legs. On August 30, forty-eight days after the onset of toxemia, the patient was dismissed. His general condition was very satisfactory.

Three and a fourth years later (Oct 24, 1935) the patient felt well. He weighed 211 pounds (96 Kg). His general physical condition was satisfactory, and his blood pressure was 190 systolic and 110 diastolic. The eyegrounds revealed mild sclerosis of the retinal arterioles. Urinalysis did not show albumin or sugar, but there were still 50 pus cells per microscopic field (table 1). The patient still had chronic pyelonephritis, with slight reduction of renal function. The hypertension was of the essential type.

CASE 2—The patient, aged 40 years, a life insurance agent, was admitted on Aug 4, 1932. Two weeks previously he began to have attacks of severe pain in the right lumbar region, which spread slightly around over the iliac crest to the right lower quadrant of the abdomen. There were mild chills and a little fever, and the pain lasted three or four hours. His local physician shortly afterward found microscopic quantities of blood in the urine. The patient's second attack was similar to the first and occurred one week before his admission to the clinic, it also lasted four hours, and microscopic quantities of blood were again passed. No stones were passed during or after either attack. Jolting when riding in an automobile caused a dull ache in the right lumbar region.

On physical examination the patient's weight was 151 pounds (68.6 Kg), his blood pressure was 130 systolic and 80 diastolic. There was no edema. The value for hemoglobin was 17.5 Gm per hundred cubic centimeters, and the erythrocytes numbered 4,520,000 per cubic millimeter. The urea content of the blood was 26 mg per hundred cubic centimeters. The urine had a specific gravity of 1.010, it contained no albumin or sugar. There were 10 leukocytes per microscopic field but no erythrocytes. A roentgenogram disclosed a small calculus in the region of the upper third of the right ureter.

On August 8 from 7 to 10 cc of the bismuth solution was injected through a ureteral catheter into the right ureter and renal pelvis. It remained there for ten or fifteen minutes and then was allowed to drain off through the catheter. A pyelogram of the right kidney was made, and the right ureter showed angulation near the sacro-iliac synchondrosis. A diagnosis of calculus in the right ureter was made. After cystoscopic examination the patient vomited 800 cc of fluid, and the next day, 450 cc.

On the third day (August 10) nausea and vomiting continued, emesis of 950 cc brought the total up to 2,200 cc for the first three days. There was acute necrotic gingivitis. On August 11 there were still nausea and vomiting, some hiccup and oliguria, 80 cc of urine having been passed in twenty-four hours (table 2). The next day the patient's mouth became sore, his gums were blue and bismuth poisoning was suspected. On August 13 solution of sodium thio-sulfate was given intravenously. His blood pressure was 170 systolic and 80 diastolic. The gums continued to be sore the next day, and ulcerating stomatitis was present. The blood pressure on this day was 145 systolic and 90 diastolic.

TABLE 2—The Data for the Second Patient

Day of Observation	Intake of Fluid				Urine†				Blood					Comment				
	Sodium Bicarbonate, Gm	Sodium Chloride, Gm	Dextrose, Gm	Total, Cc	Total Intake of Fluid, Cc	Volume, Cc	Protein, Grade	Casts, Grade	Erythrocytes, Grade	Leucocytes, Grade	Hemoglobin, Gm per 100 Cc	Erythrocytes, Millions per Cu Mm	Urea, Mg per 100 Cc		Creatinine, Mg per 100 Cc	Plasma Cholesterol, Mg per 100 Cc †	Plasma Carbon Dioxide Combining Power, Vol %	
1																		Roentgenogram of kidneys, ureters, bladder, small ureteral stone on right
3				1,500	3,900	80												Pyelogram of right kidney
4				1,500	4,100	500	3	0	0	4			132	9.0	462	39		Acute gingivitis
5				1,700	4,300	500	2	1	0	0			142					Blue gums
6				1,500	4,500	510												Sodium thiosulfate 1 Gm §
7					2,600	500												Stomatitis
8		16.2		1,800	3,900	350							165	14.4				Ureteral stone passed
9	25		200	2,500	2,900	460	1	2	0	0			189	15.2	453	43		Sodium thiosulfate, 1 Gm §
10			187	1,875	2,675	1,600	2	1	3	1			162	16.0	479	46		
11		3.6	100	1,400	2,155	2,240							177	16.0				Sodium thiosulfate, 1 Gm §
12		10.0	100	1,000	3,500	4,200							171	15.2	495	48		
13		4.5	100	1,500	3,910	4,900	2	0	0	0								
14		1.0	100	1,120	3,720	5,140							141	11.2				Wrote that he felt was excellent
15					3,600	4,600							162	8.4	511	33		
16		10.0		1,000	3,900	4,220							120	6.0				
17					2,900	3,580							96					
22, 1½ years later																		

* Data obtained on entry

† Variation of the specific gravity during toxemia, 1.004 to 1.010

‡ Calculated as sodium chloride

§ Ten cubic centimeters of 10 per cent solution injected intravenously

On August 16 the patient passed a ureteral stone. Daily readings of the blood pressure taken from August 16 to 24 showed variations, the systolic pressure being from 110 to 170 and the diastolic from 60 to 100 mm of mercury. On August 19 slight edema of the scrotum and inner portions of both thighs appeared. Sodium thiosulfate was given intravenously. The gums were still sore and the temperature had varied since the onset of toxemia from 98 to 101 F. On August 29, twenty-two days after the onset of toxemia, the patient felt well, the urinary output was satisfactory and the value for blood urea was 36 mg per hundred cubic centimeters.

On Dec 30, 1935, approximately three and a half years after the acute toxemia, the patient wrote that he was in excellent health.

COURSE OF TOXEMIA

The acute toxemia in these two cases was characterized by the rapid development of oliguria or anuria within from twenty-four to forty-eight hours after the injection of the bismuth solution. Oliguria was accompanied with nausea and vomiting. Three or four days after the onset, bleeding from the gums and stomatitis developed, but discoloration of the buccal mucous membrane was not evident for several days. The serious disturbance of renal function was accompanied with only minor changes in the amount of protein and sediment in the urine, albumin (grade 2) was present, and there were a few hyaline and granular casts. Erythrocytes were present in the urine of the first patient after renal decapsulation and in the urine of the second patient after passage of the ureteral calculus. The development of azotemia was rapid, and by the fourth day in the second case the values for blood urea and creatinine had risen to 132 and 9 mg per hundred cubic centimeters respectively. The values for the first patient were slightly lower. Azotemia continued for a period of approximately three weeks, the maximal concentration of urea and creatinine in the blood being 234 and 14 mg per hundred cubic centimeters, respectively, in the first case and 189 and 16 mg, respectively, in the second. During the period of oliguria and nitrogen retention a moderate decrease in the bicarbonate reserve of the plasma and a decided fall in the chloride concentration of the plasma occurred. Comparable findings have been reported in cases of poisoning due to mercury bichloride⁶ and chromium trioxide⁷ and of other types of acute renal insufficiency.⁸

At the height of the toxemia the first patient became irrational and twitchings of the facial muscles lasted for several hours. The gradual

6 Lewis, D. S., and Rivers, T. M. Chemical Studies on a Case of Bichloride Poisoning, *Bull Johns Hopkins Hosp* **27** 193-201 (July) 1916.

7 Major, R. H. Studies on a Case of Chronic Acid Nephritis, *Bull Johns Hopkins Hosp* **33** 56-61 (Feb) 1922.

8 Keith, N. M., and Thomson, W. W. D. War Nephritis. A Clinical, Functional, and Pathological Study, *Quart J Med* **11** 229-266 (April) 1918.

development of dependent edema was due in part to the large intake of water and sodium chloride and the small output of urine. With resumption of an adequate urinary output, the edema rapidly disappeared. The temperature was usually normal, although in each case it rose on one occasion to 101 F, a rise which may have been due to stomatitis. Daily estimations of the blood pressure were made, and the systolic and diastolic pressures were usually within normal limits. The reason the systolic blood pressure rose to 170 mm of mercury once in each case is difficult to explain. From three to six weeks after the onset the urea content of the blood reached a normal concentration, and the patients appeared and felt well. The course of the acute renal insufficiency in these cases was similar to that due to mercury bichloride and other agents toxic to the renal parenchyma. Raiziss and Brown⁹ noted in a study of the toxicity of bismuth in rabbits that recovery of normal renal function occurred within approximately one month after a toxic dose was received.

Both of our patients were in excellent general health three years later. The first patient returned at this time, and renal function was found to be satisfactory.

TREATMENT

At the onset of the toxemia our therapeutic objectives were to increase renal excretion and prevent dehydration. Because of vomiting, much of the fluid necessarily was injected intravenously. The solutions given were 1 per cent sodium chloride, from 5 to 10 per cent dextrose and 5 per cent sodium bicarbonate, and the daily amounts injected were from 1,000 to 3,000 cc. In our opinion these intravenous injections of appropriate fluid constituted the most important therapeutic measure. In the first case the injection of a small amount of salyrgan on two occasions had no apparent beneficial or harmful effect. Bilateral renal decapsulation did not cause an immediate increase in the volume of urine, nor was an adequate renal output restored until six days after the operation. In the second case the injections of sodium thiosulfate did not appear to affect the toxemia.

TOXICITY OF BISMUTH SOLUTION

In the first case there is the possibility that a considerable portion of the 150 cc of bismuth solution that was injected into the bladder may have entered the vascular system. In such an event the actual

⁹ Raiziss, G. W., and Brown, H. Toxicity and Reactions Caused by Arsphenamin and Neo-Arsphenamin. The Effect of Organic Compounds of Arsenic, Mercury and Bismuth on the Kidneys of Animals, Judged by the Non-protein Nitrogen and Urea Content of the Blood, *Arch. Dermat. & Syph.* **10** 1-13 (July) 1924.

amount of bismuth salt circulating in the blood stream might have been sufficient to cause the toxemia. On the other hand, the volume of bismuth solution, from 7 to 10 cc, that entered the ureter and renal pelvis in the second case seems too small to have been the sole cause of the toxic effects. The possible presence, however, of more highly toxic bismuth compounds in the solution must be duly considered.¹⁰ Another factor to be reckoned with was the presence of renal changes, which might have allowed greater absorption and systemic circulation of the toxic compound, resulting in general toxemia. The data in the present study do not warrant a definite conclusion as to whether the toxemia was due to the bismuth salt itself or to more highly toxic bismuth compounds acting on pathologic renal tissue. A combination of these factors seems most probable.

COMMENT

Twenty-five years ago poisoning due to bismuth subnitrate occurred not infrequently.¹¹ This substance, a medium opaque to roentgen rays, was employed as a diagnostic aid in investigating suspected lesions in the gastro-intestinal tract, it was used also in dusting powders and pastes, as for example in paste of bismuth N F, to secure the healing of wounds and infected sinus tracts.¹² With the development of toxemia, cyanosis due to methemoglobinemia was often present.¹³ Since one of us,¹⁴ while investigating the diuretic properties of ammonium nitrate in 1928, observed transient methemoglobinemia in two cases, without alarming or uncomfortable symptoms, and rapid disappearance of the cyanosis when the administration of the salt was discontinued, we have been of the opinion that the serious toxic symptoms of bismuth subnitrate poisoning have been due to the bismuth rather than to the

10 Leonard, C. S. Studies in the Pharmacology of Bismuth Salts. II. Toxicity and Urinary Elimination of Soluble Bismuth Salts, *J. Pharmacol. & Exper. Therap.* **28** 89-108 (July) 1926. Leonard, C. S., and O'Brien, J. L. Studies in Pharmacology of Bismuth Salts. III. Toxicity and Urinary Elimination of Potassium Bismuth Tartrate, *ibid.* **28** 109-119 (July) 1926.

11 Cabot, R. C. Bismuth Poisoning, with Report of a Case, *Tr. A. Am. Physicians* **27** 457-470, 1912. Mayer, Leo, and Baehr, George. Bismuth Poisoning. A Clinical and Pathological Report, *Surg., Gynec. & Obst.* **15** 309-322 (Sept.) 1912. Warfield, L. M. Bismuth Poisoning, *Am. J. M. Sc.* **144** 647-658 (Nov.) 1912.

12 Higgins, W. H. Systemic Poisoning with Bismuth, *J. A. M. A.* **66** 648-650 (Feb. 26) 1916.

13 Phillips, John. Bismuth Poisoning and Nitrate Poisoning from the Use of Bismuth Subnitrate, with Report of Three Cases, *Cleveland M. J.* **16** 419-428 (June) 1917.

14 Eusterman, G. B., and Keith, N. M. Transient Methemoglobinemia Following Administration of Ammonium Nitrate, *M. Clin. North America* **12** 1489-1496 (May) 1929.

nitrate radical. The two present cases, in which toxemia was undoubtedly due to bismuth, lend further support to such an explanation.

The acute onset of oliguria and stomatitis suggests poisoning by a heavy metal. Mercury bichloride is the most common agent causing such a syndrome that one meets clinically. Stomatitis due to bismuth intoxication can be distinguished from that due to mercury compounds by the gradual development of blue-black areas of discoloration on the gums and buccal mucous membrane. It is of interest also to point out that in acute lead poisoning, which one might consider if confronted with the symptoms observed in bismuth intoxication, renal insufficiency does not occur.¹⁵ This absence of renal damage in acute intoxication due to lead was strikingly apparent to a group of those in the clinic administering lead compounds therapeutically in cases of various types of advanced malignant growths. In concluding this report we wish to stress the importance of considering bismuth intoxication as a possible etiologic factor whenever there are rapidly developing oliguria and stomatitis.

15 Horton, B. T., Borgen, J. A., and Osterberg, A. E. Personal communication to the authors.

INHERITANCE OF THE SHAKING PALSY

WILLIAM ALLAN, M D

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Shaking palsy, first adequately described by Parkinson¹ in 1817 and since generally known as Parkinson's disease, appears mostly in persons in the latter half of life. It is characterized by muscular rigidity and weakness, tremor, a propulsive gait and masklike facies, without disturbances of sensation or reflexes. The most striking symptom, tremor, is characterized by short oscillations of the head or extremities at the rate of from 4 to 7 a second and is most pronounced during rest, as contrasted with the intention tremors of senility and of multiple sclerosis.

According to J Ramsay Hunt,² "Paralysis agitans is not a disease *suu generis* but a syndrome referable to the efferent neurons of the corpus striatum (striatal and pallidal). This syndrome may be produced by a variety of pathologic lesions, viz, primary atrophy, senile degeneration, and vascular, inflammatory and neoplastic lesions. Therefore, primary and secondary forms are recognized."

Medical authorities³ suggest various causes for this syndrome, such as prolonged physical strain, emotion, trauma and exposure to cold, but there is no evidence to show that these factors are important.⁴ Heredity is mentioned as a causative factor by some authors and overlooked or denied by others. In investigating the hereditary factor in shaking palsy, manifestly the cases in which it is due to inflammation or to neoplasm need not be considered.

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1 Parkinson, cited by Osheimer, A J. An Essay on the Shaking Palsy, by James Parkinson, M D, Member of the Royal College of Surgeons, Arch Neurol & Psychiat 7 681 (June) 1922.

2 Hunt, J Ramsay. Primary Paralysis Agitans, Arch Neurol & Psychiat 30 1332 (Nov) 1933.

3 McCarthy, D J, in Osler, W, and McCrae, T. Modern Medicine, Philadelphia, Lea & Febiger, 1928, vol 6, p 767.

4 Grimberg, L. Paralysis Agitans and Trauma, J Nerv & Ment Dis 79 14 (Jan) 1934.

Gowers and Berger each found a family history for 15 per cent of their patients,⁵ and Patrick and Levy⁶ found evidence of direct inheritance for 6 of 146 patients. Bell and Clark,⁶ in 1926, reported a pedigree and gathered reports of 9 other families from the literature. These 10 pedigrees, with 1 published by Kuckens,⁷ constitute all the data so far published on which to base an opinion as to the inheritance of shaking palsy. Two of these pedigrees showed palsy in 1 parent and 1 or 2 children, 3 showed it in a single fraternity, and 1 showed it in 7 of 9 sibs, with 3 instances in the second generation. Kuckens' pedigree embraced three generations, and there were 3 pedigrees running through three or four generations that were indicative of a dominant trait, but the pedigree published by Lundborg, embracing three generations, suggested a recessive trait.⁸

Because of the paucity and conflicting nature of this evidence, I have examined 72 consecutive patients with the parkinsonian syndrome from whom it was possible to secure an adequate family history. In 7 cases there was no family history of this disorder but a past history of probable encephalitis, in 20 cases neither the family nor the past history offered an explanation of the syndrome, in 45 cases near relatives, parents, siblings or children, had the same disorder. For only 24 of the 45 patients with a history of palsy was the family history complete, and the charts showing these pedigrees are reproduced here (charts 1 to 24).

A summary of the data presented in these pedigrees shows a sex ratio of 3 men to 2 women (153 to 105), which is the same ratio reported by Patrick and Levy. There are several instances in which both men and women have been married twice to partners without palsy and have passed the trait on to both sets of children. The preponderance of men is not due to sex linkage but is possibly caused by some environmental factor.

There are 79 instances in which the trait was present in the children and in 1 parent (father, 43, mother, 36). The appearance of

5 Patrick, H. T., and Levy, D. M. Parkinson's Disease, *Arch Neurol & Psychiat* **7** 711 (June) 1922.

6 Bell, Julia, and Clark, A. J. A Pedigree of Paralysis Agitans, *Ann Eugenics* **1** 455 (April) 1926.

7 Kuckens, H. Ueber Heredofamiliarität bei Paralysis agitans, zugleich ein Beitrag zum hereditär bedingten Auftreten des Diabetes mellitus bei einengen Zwillingen, *Klin Wchnschr* **4** 2289 (Nov 26) 1925.

8 Baur, E., Fischer, E., and Lenz, F. Human Heredity, New York, The Macmillan Company, 1931, p. 417.

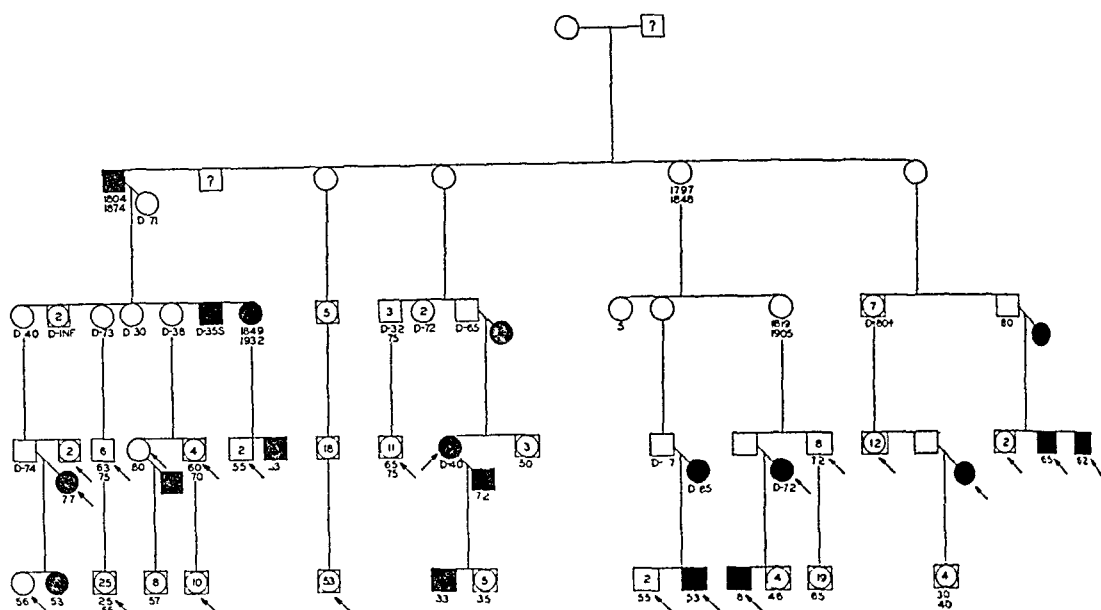


Chart 1—In charts 1 to 24 a square indicates a male, a circle, a female, and a square and circle combined, both sexes. A black square or circle indicates palsy, and a question mark, status with regard to palsy not known. A number within a square, circle or combined square and circle indicates the total number of children represented, a number appearing below a square or circle, the age, *D* followed by a number, the age at time of death, *D—Inf* died in infancy, *S* single, arrows, the members whom I have seen.

McD (I, 2) emigrated from Scotland and settled in Mecklenburg County, N C., about the time of the Revolutionary War. By his first marriage he had 2 sons and 4 daughters. One son, the second member of the second generation (II, 2), moved across the mountains to Tennessee and was lost track of, the other son (II, 1) died at the age of 71 and is reported by many of his grandchildren to have had shaking palsy severely. None of the grandchildren and great grandchildren of McD's 4 daughters by this marriage have had palsy unless it was introduced into the family by marriage. The first son in generation II (II, 1) had 8 children, 2 (III, 2) dying in infancy and 3 married daughters dying before the age of 40 (III, 1, 4 and 5). One of these daughters died childless, the other 2 left 8 children, 4 of whom, all over 65, I examined and found without tremor. A fourth daughter of II, 1 lived to be over 70. She left 6 children who lived to be over 63, 2 of whom I have seen. There is no palsy in the descendants of these daughters. III, 6, the son of II, 1 showed palsy early and died a bachelor at the age of 35. The sixth daughter (III, 7) died at the age of 83 with palsy, and 1 of her 3 sons (IV, 7), aged 53, has palsy. In generation III there were 2 men who married wives with palsy (half first cousins), and the trait appeared in their children (IV, 10, 18 and 19). Six members of generation IV married partners with palsy (cousins in 5 instances), and palsy has appeared in the children of 4 of these couples. The oldest children of the other 2 couples are 57 and 40 years old, respectively (V, 4 and 14).

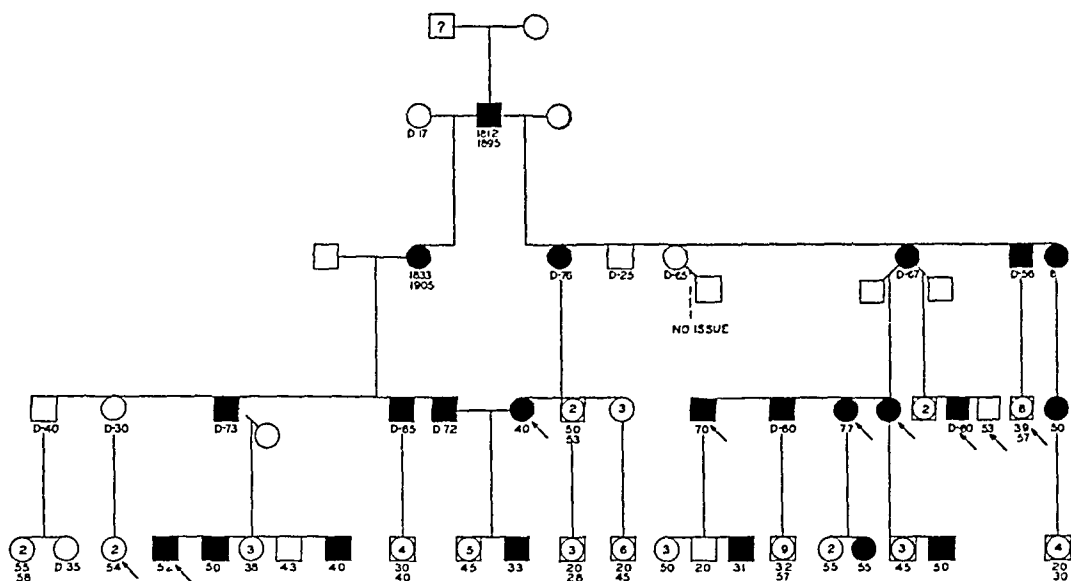


Chart 2—McD's second marriage resulted in 1 son (II, 2), who died at the age of 83 with palsy, as reported by several of his grandchildren. This son married four times, raising 2 sets of children. By his first wife there was 1 daughter (III, 2) who died at the age of 72 with palsy. She left 5 children (IV, 1 to 5). Two of these children died when 30 and 40 years old, respectively, and none of their children (V, 1 to 3), the oldest being 58, have as yet shown any tremor. III, 2's other 3 children (IV, 3 to 5) all had palsy, and the malady has reappeared in the children (V, 4, 5, 8 and 11) of 2 (IV, 3 and 5). The children of the third son (IV, 4) are still under 40. McD's son's second marriage resulted in 6 children, 1 of whom died young and unmarried, 4 had palsy and 1 did not. One of the palsied daughters (III, 3) has passed the trait to 1 of 3 children reaching the age of 50, another (III, 6) has raised 2 sets of children, and palsy has appeared in both sets (IV, 9 to 12 and 14), a third child with palsy (III, 7) had 8 children, the oldest now 57, but so far none is palsied. The fourth child with palsy (III, 8) passed it to her only child (IV, 17). IV, 10 left 9 children, the oldest now 57, none of whom is palsied. The 42 affected members of this family are about equally divided as to sex, 24 men and 18 women. The trait has descended through both men (4) and women (12) and has appeared in both sets of children when both an affected mother and an affected father have married twice.

The collateral descendants of both of McD's wives and both of the wives of his son by his second marriage live in Mecklenburg County, N. C., and do not have palsy.

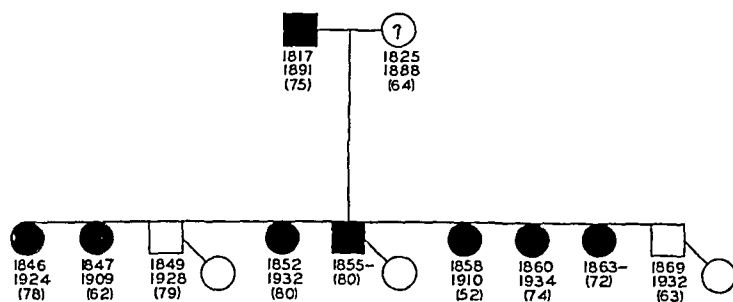


Chart 3—This is the only family that has refused to cooperate, information had to be obtained from friends and the family physician. The father and 7 of 9 children were palsied, 6 of them never married.

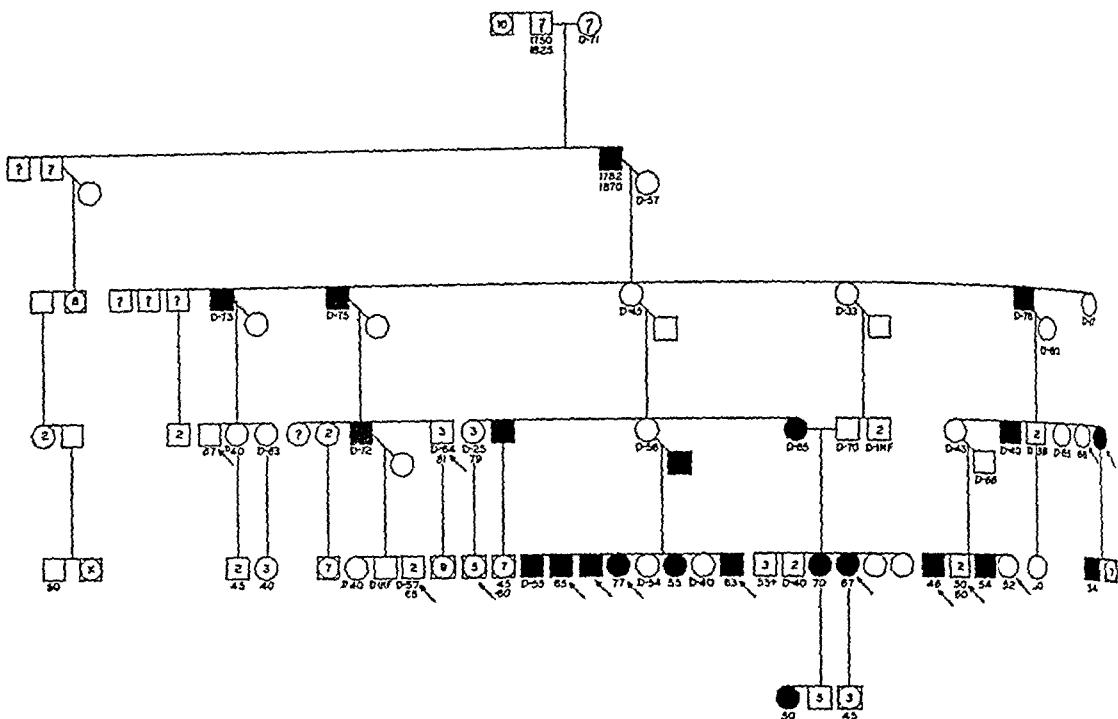


Chart 4—The ancestor of this family (I, 2) moved from Augusta County, Va, to Mecklenburg County, N C, before the Revolutionary War and died in 1825. There is no memory of him among his descendants. There were 3 sons, James (II, 1), of whom there is no record, John (II, 2), whose grandchildren have no palsy, and William (III, 3), 1782-1870, whose grandchildren report that 1 slave's sole duty was to feed and care for the palsied old man. William left 9 children, 3 sons (III, 3 to 5) moved to Tennessee, and nothing further is known about them. Of the 6 children remaining in North Carolina, the 3 sons all lived to be over 73, and all had shaking palsy. The oldest son (III, 6) had 3 children, a son (IV, 4), now 67, without palsy and childless, and 2 daughters (IV, 5 and 6), who died at 40 and 63 years of age, without palsy. The grandchildren are not over 45. The fifth son (III, 7) of II, 3 left 7 children, 1 of whom I interviewed when he was aged 81. One daughter (IV, 7) moved west, and only 1 (IV, 9) of the 6 remaining children is reported to have had palsy. IV, 9 left 4 children, 2 of whom died before reaching 40, 1 died while under my care when he was 57, without palsy, and the other writes me that he has no sign of palsy at the age of 68. II, 3's oldest daughter (III, 8) died in 1860, when 45 years old. She was too young to show palsy, but as 2 of her children (IV, 12 and 14) had palsy, she doubtless transmitted the trait. The oldest daughter (IV, 11) of III, 8 died when 79 and left 2 sons, now 58 and 56, all without palsy. III, 8's oldest son had palsy, but none of his 7 children, the oldest being 60 has it so far. Two of III, 8's daughters (IV, 11) died young without palsy, 1 leaving 2 sons, who died young and unmarried, and the other leaving 1 daughter, who died when 69 without palsy. III, 8's fourth daughter (IV, 13) died when 56 without palsy, she had married a man in whom palsy developed and left 8 children (V, 12 to 19) 6 of whom, above the age of 55, have palsy. Two children died at the age of 40 and 54, respectively, without showing palsy. Because so many of these children have palsy, it seems likely that IV, 13 carried the trait. III, 8's youngest daughter (IV, 14) died at the age of 85 with palsy, and of her 9 children, 2 died before reaching 40, 2 have palsy and 5 have no palsy as yet. III, 9 died at the age of 33 without palsy, leaving 3 children (IV, 15 and 16), of whom 2 died young and childless without palsy and 1 died at the age of 70 without palsy. III, 10 died at the age of 78 with palsy, leaving 7 children. The oldest child (IV, 17) died at the age of 43 without palsy, but as 2 of her 5 children already show palsy and there is no sign of palsy in her husband's family, it seems reasonable to assume that she carried the trait. The second child (IV, 18) of III, 10 died childless at the age of 40 with palsy. A third child died childless when 38 without palsy, and a fourth (IV, 19) died when 40 without palsy, leaving 1 daughter, who does not show signs of palsy at the age of 50. Two of III, 10's single daughters (IV, 20 and 21) passed the age of 65 without palsy, but her youngest daughter (IV, 22) has palsy at the age of 65, and 1 of the latter's children has it. In the seventh generation there is 1 instance of palsy in a person aged 50. X for V, 2 indicates number of children unknown.

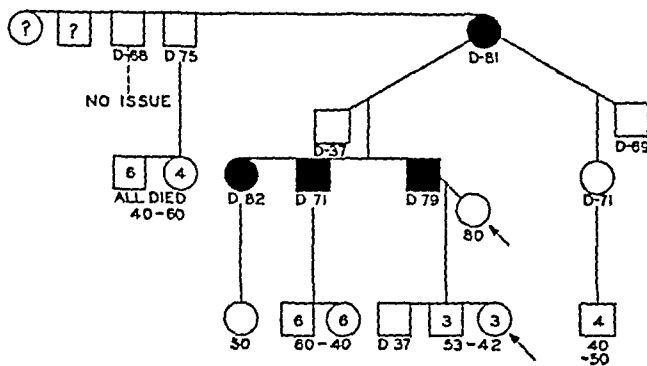


Chart 5—Two brothers (II, 4 and 5) were known to have palsy. The widow of 1 of them gave me the pedigree. II, 3 left 1 daughter, now aged 50, without palsy. II, 4 left 12 children, the oldest now being aged 60, none of whom has yet shown signs of palsy. II, 5 left 7 children, 1 of whom died at the age of 37, the oldest of the remaining 6 being now 53—all without palsy.

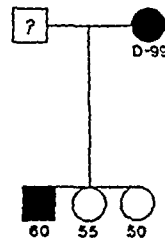
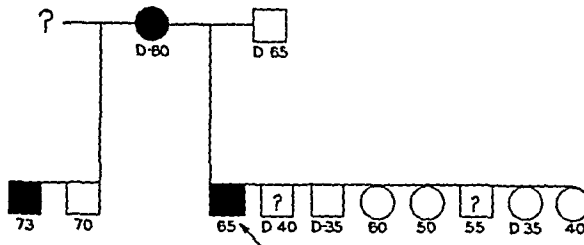


Chart 6—Parkinson's disease is rare in the Negro. The first of these pedigrees was given me by an old serving man (II, 3) whose tremor while waiting on my table nearly caused him to spill the food. From the shape of his head and features, I think he is not pure African. The second pedigree was given me by Dr. H. C. Neblett, of Charlotte, N. C., who knew both the mother and the son with palsy.

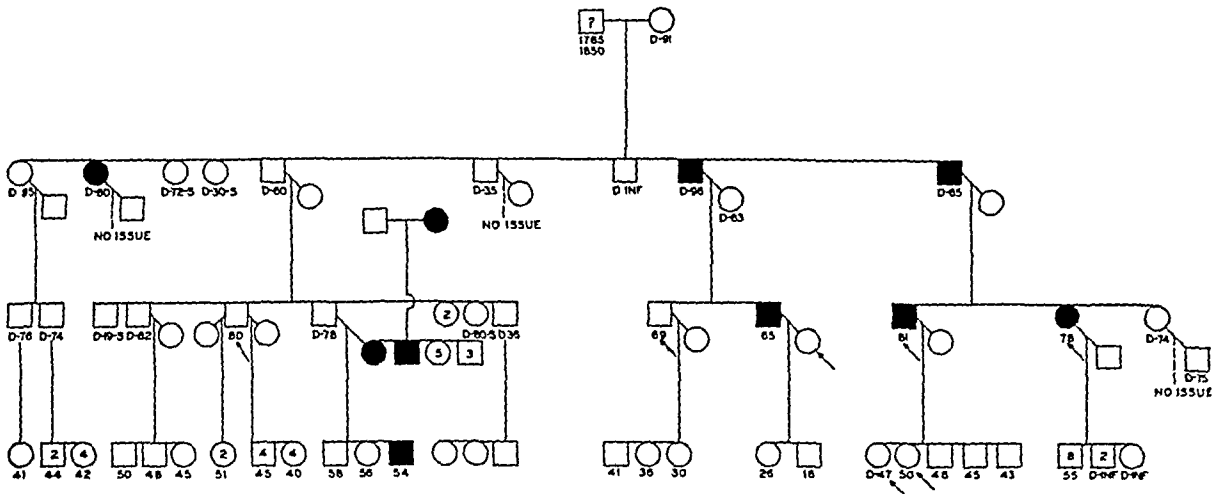


Chart 7—This is a Lincoln County family, descendants of German immigrants who settled there two hundred years ago. Three members of the third generation around the age of 80 were examined, but none of them remembered the grandfather, who died in 1850. Three of the 6 members of the second generation who passed the half century mark had palsy. Three of 5 possibilities in the third generation have palsy, and 1 member of the fourth generation already has it at the age of 54.

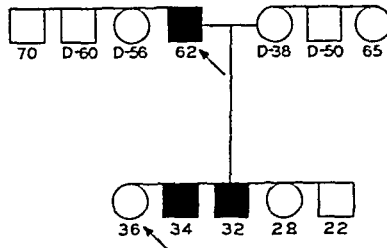


Chart 8—As the propositus (I, 4) moved into Charlotte, N C, from the tide-water section, it was not possible to extend this pedigree Tremor developed when he was about 45, and in 2 of his children in the fourth decade palsy is developing

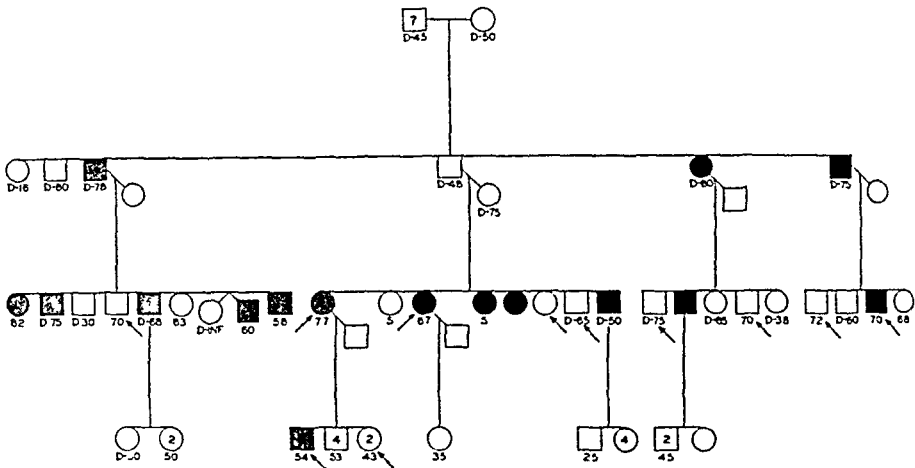


Chart 9—The members of the first generation of this Mecklenburg County family died at about 50 years of age, and no one now remembers them In the second generation 1 son (II, 4) died at the age of 48 without palsy, but as 5 of his 8 children had palsy it is likely that the trait descended through him

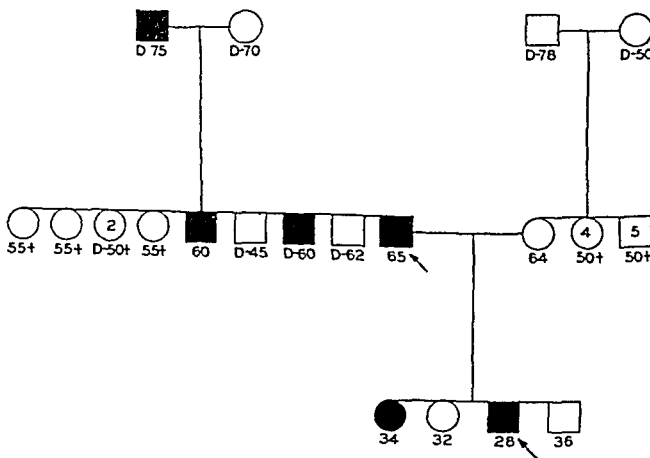


Chart 10—III, 3 has moved to Charlotte, N C, from the eastern part of the state His father (II, 9) was interviewed while visiting the son and confirmed the pedigree

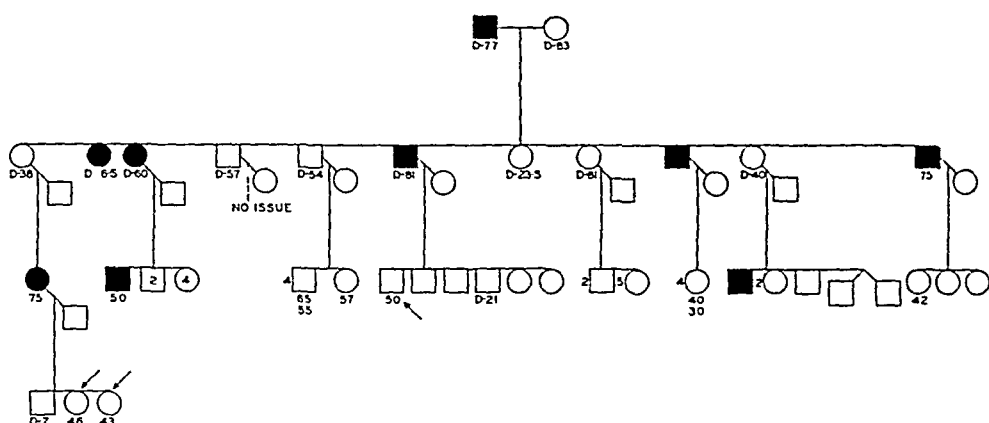


Chart 11—I secured the pedigree of this Richmond County family from several members of the third and fourth generation and later had it confirmed by some physicians who had known members of all four generations II, 1 and 10 died at the age of 40 without palsy, which has developed in the children of both of them, so that they doubtless transmitted the trait

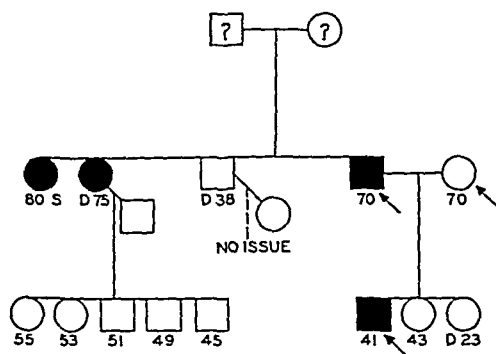


Chart 12—This Montgomery County family knew nothing of the previous generations

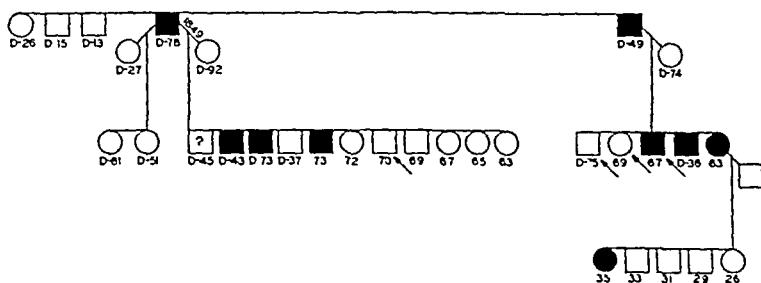


Chart 13—In this Stanley County family I, 4 transmitted palsy to only 1 set of children

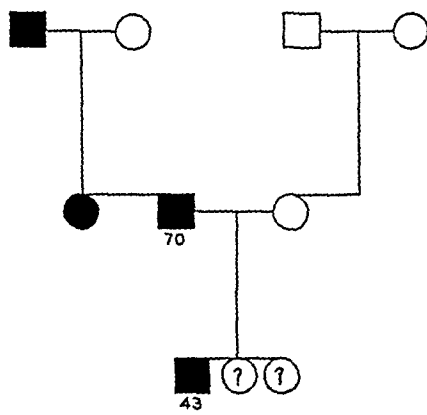


Chart 16—This pedigree was sent to me by Dr Tilman Ramsey, of Kentucky, and I cannot enlarge on it

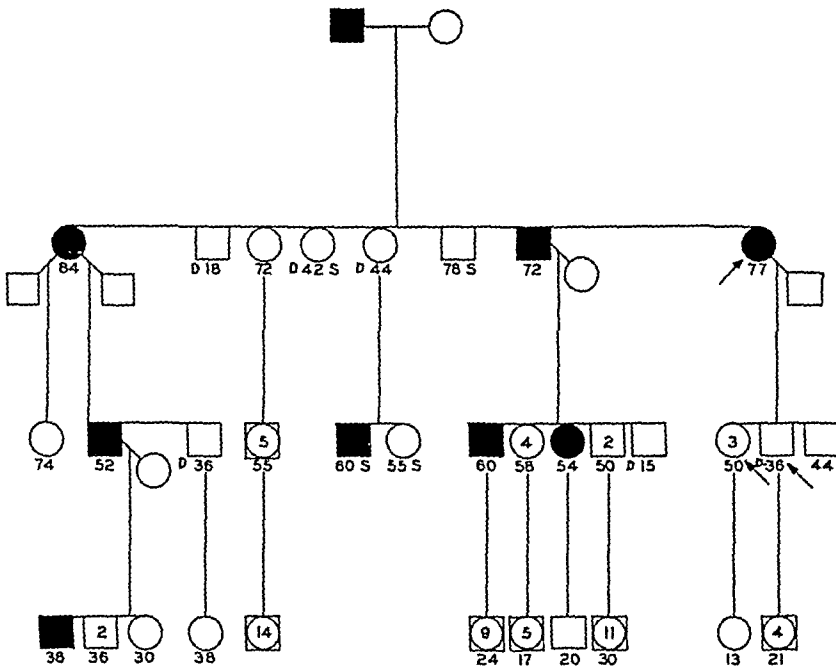


Chart 17—The pedigree of this Burke County family, coming originally from Powhatan County, Va, was supplied by II, 8, who has been a patient of mine for a number of years. Since the son of II, 5, has palsy, I judge his mother, who died when 44, carried the trait

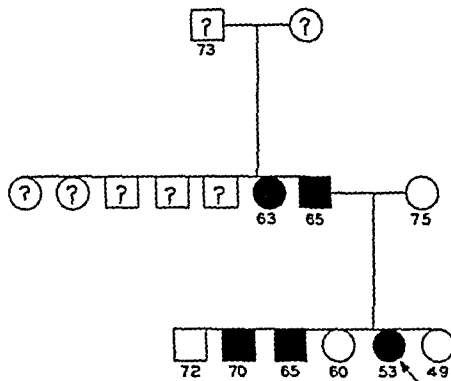
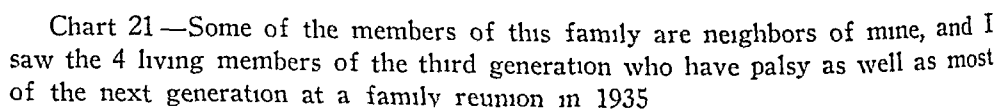
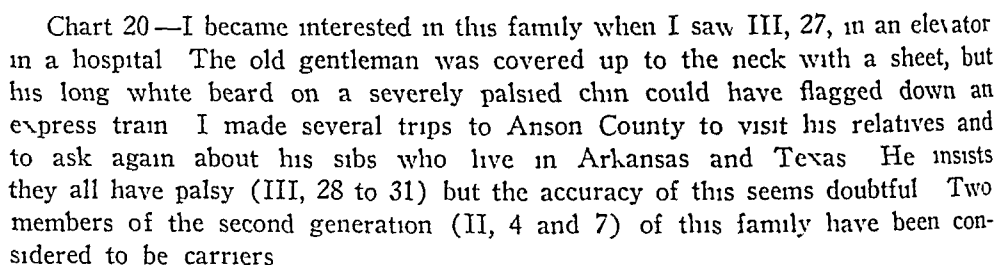
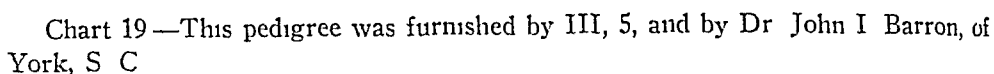


Chart 18—This pedigree of a South Carolina family was supplied by III, 5, who knew little about her father's sibs and parents



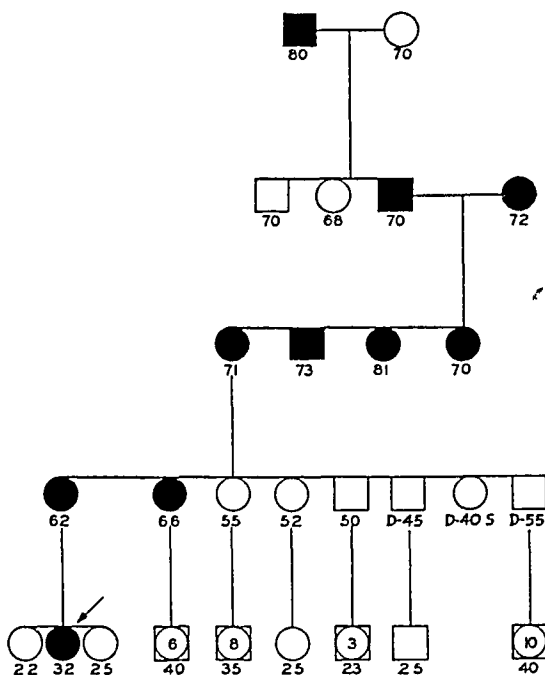


Chart 22—V, 2 was sent to me because of marked shaking palsy With the help of her mother she worked out the pedigree of this Georgia family

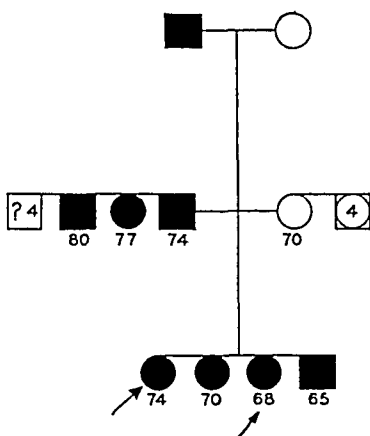


Chart 23—This pedigree of a South Carolina family was given to me by III, 1 As usual, pedigrees supplied by a single member of a family are not extensive

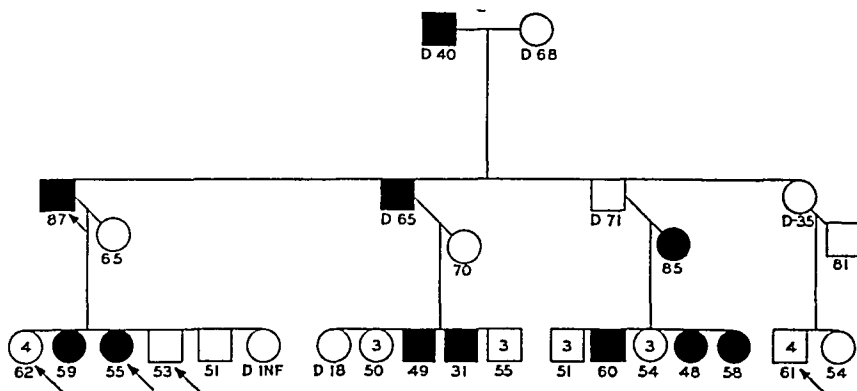


Chart 24—This pedigree of a Mecklenburg County family was supplied by II, 1 and his children I have seen palsy in members of other branches of this large clan

shaking palsy in any person depends largely on age, as demonstrated by Patrick and Levy's table showing the time of onset

Age, Years	Percentage
21-30	3.4
31-40	13.7
41-50	28.0
	<hr/> 45.1
51-60	33.6
61-70	18.6
71-80	2.7
	<hr/> 100.0

Bell and Clark in a compilation of 423 cases found the average age of onset to be 52.4 years. One half (146) of the 290 children of 79 parents who lived to be over 50 had palsy.

In 36 instances palsy was present in a parent but not in the children. In 28 of these families the children were under 50 years of age, in the remaining 8 families only 15 of the 47 children had reached the age of 50.

In 8 instances there was skipping of a generation, 6 of the parents were under 50, 1 was 54 and 1 was 56.

Six whole sibships were reported as having palsy, 1 of these fraternities lives in North Carolina, but the members of the other 5 are scattered from Arkansas to Kentucky, and the history could not be verified by examination. In 2 other families a similar history was found to be incorrect when all the members of the fraternities were examined, so such a history is of doubtful accuracy.

In three instances both parents were reported as having palsy, in 1 instance there were 6 children under 40, with 1 affected, in 1 all 4 children lived to be over 70 and were affected (Georgia), in 1 all 4 children, aged 27 to 33, were said by the father to be affected.

The majority of these pedigrees could be greatly enlarged were sufficient time and effort applied to the task. However, the material that has been gathered in the course of daily practice and presented here demonstrates beyond doubt the important rôle played by heredity in the incidence of shaking palsy.

CONCLUSION

Although the occasional failure of shaking palsy to appear in the children of palsied parents and the skipping of generations, with the history of entire fraternities being affected, suggest recessiveness of this trait, the greater weight of the evidence indicates that in about two thirds of the cases studied in North Carolina shaking palsy was inherited as a dominant trait, probably conditioned by a single autosomal gene.

PULSATIONS OF THE WALL OF THE CHEST

II PULSATIONS ASSOCIATED WITH AORTIC REGURGITATION

WILHELM DRESSLER, M D

VIENNA, AUSTRIA

In the presence of aortic regurgitation the left ventricle is dilated and does an increased amount of work. This leads to the formation of a strong cardiac thrust, which may range from a circumscribed increased apical thrust to a diffuse bulge of the precordium. The formation of this bulge is not rarely interfered with by the effect of systolic aspiration (regarding the reduction of the ventricular volume during the systolic efflux), which may reach a marked degree with this type of valvular lesion. An abnormally large quantity of blood flows during systole from the dilated left ventricle into the arteries, and the bulk of it leaves the thorax, resulting in a rapid fall in intrathoracic pressure. So far as this condition is not compensated for by the inspiratory movement of the column of air within the lungs, two means of compensation are available: first, by an increased aspiration of venous blood into the chest and, second, by a reduction of the intrathoracic space, i. e., by a flattening of the ventral wall. A diffuse depression of the ventral wall of the chest is therefore not rarely encountered in the presence of aortic regurgitation, this was first described by Lang¹ and later by Ortner,² and personal investigations led to the same findings in not a few cases.³ This pulsatory phenomenon, however, is not a constant finding. Occasionally it is missed entirely, and if present, there is considerable variation as to extent and degree of depression of the thoracic wall. The varying appearance of pulsations in aortic regurgitation depends on several factors, the causal interplay of which may not always be clear in a given case.

The intensity of pulsations over the heart as well as over the hepatic area depends on the degree of the valvular lesion, and that means on the amount of blood which during systole disappears from the thoracic cavity and on the abruptness of the fall in pressure. The faster the

Translated by Hugo Roesler, M D, Philadelphia

From the *Herzstation*, Dr. Hans Horst Meyer and Dr. Emil Zak, directors

1 Lang, G. Ueber einige durch die Herzaktion verursachte Bewegungen der Brustwand und des Epigastriums, *Deutsches Arch. f. klin. Med.* **108** 35, 1912

2 Ortner, N. Physikalische Erscheinungen in der Präcordialgegend und deren Deutung, *Med. Klin.* **25** 63, 1929

3 Dressler, W. Die Brustwandpulsationen als Symptome von Herz und Gefasskrankheiten, Vienna, Wilhelm Maudrich, 1933

blood leaves the thoracic cavity, the less closely will the inspiration of air into the lungs and the relatively slow influx of venous blood keep pace with it, and the more strongly will aspiration act on the wall of the chest. In addition, varying conditions of the lungs, their capacity for expansion and the elasticity of the bony skeleton will influence the formation of the pulsatory picture.

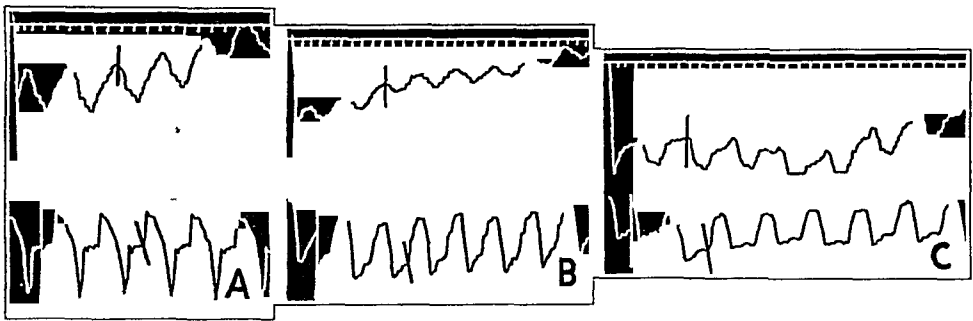
The effect of systolic aspiration of the thoracic wall is often partly or completely neutralized by the opposing force of the systolic change in shape of the heart, as expressed, for instance, by the more forceful cardiac thrust. One therefore finds in certain cases of aortic regurgitation a diffuse propulsion of the precordial area instead of a systolic depression. One often finds a well marked systolic depression mesial to the forceful apical thrust, this leads to a peculiar seesaw movement. It must be emphasized that the systolic depression affects several intercostal spaces and extends in instances of high grade valvular defect far beyond the cardiac area, over the whole left side of the chest and at the right to the parasternal line. This diffuse depression must not be confused with the localized systolic depression which is commonly noted in the immediate vicinity of a forceful apical thrust. I assume, in accord with Mosso, that the propulsion of the thoracic wall due to the impact of the left ventricle is of significance for the development of the diffuse depression, in addition to the marked systole. This concept is supported by the fact that the graph of the movement of the thoracic wall shows a definite dip at the very beginning of the systole during the isometric period, hence at a time at which the systolic aspiratory effect could not play a rôle.

The systolic depression of the thoracic wall is followed by a ventral diastolic movement, which is rather slow, in contrast to the condition in certain cases of adhesive pericardial disease and tricuspid regurgitation, in which the systolic depression is followed by a jerky rebound of the thoracic wall. Lang has pointed out that in the latter conditions a forceful apical thrust is absent and that therefore the centripetal systolic as well as the centrifugal diastolic forces act without inhibition, whereas in aortic regurgitation, subsequent to the forceful systolic apical thrust, there results a diastolic centripetal movement of the wall which interferes with the predominant centrifugal impulses.

Ortner likewise has directed attention to the diffuse systolic depression in aortic regurgitation and has stated that this finding is noted only in cases of valvular lesions of endocarditic origin, while it is missing in cases of regurgitation of syphilitic etiology. I cannot subscribe to this statement, because my colleagues and I have found the systolic depression of the ventral wall of the chest in not a few cases of syphilitic aortic regurgitation, and the depression was not less marked

than that observed in cases in which there was a rheumatic etiology. The following case may serve as an example.

R. J., a man aged 61, had syphilitic aortic regurgitation with considerable limitation of physical capacity. Examination revealed that the cardiac area bulged definitely. The apical thrust, which was noted in the sixth intercostal space, 1 inch (2.5 cm) outside the left midclavicular line, was widened and heaving. The adjacent portions of the sixth and seventh ribs showed extensive movement. Marked systolic depression was noted mesiad to the apical thrust, affecting both soft tissues and ribs. Cephalad it reached to the third rib and caudad to the costal arch; it was more marked at the level of the fourth and fifth ribs (fig. A). This depression was still felt over the sternum (figs. B and C) and over the parasternal portions at the right. The intensity diminished toward the left midclavicular line, owing to the counteracting effect of the systolic lift of the apical thrust. The epigastrium likewise was drawn in during systole. A definite seesaw movement could be felt by palpating the apical thrust with the right hand and placing the left hand with slight pressure over the precordium near the left sternal border. Percussion revealed that the area of cardiac dullness slightly exceeded the right sternal border. The lower sternal area did not reveal an increased flatness. The



The graph demonstrates the systolic depression of the precordium in a case of aortic regurgitation. The lower graph (in all the tracings) shows the apical thrust. The upper graphs were made with the receiver over, A, the left parasternal line in the fourth intercostal space, B, over the upper portion of the sternum and, C, over the lower portion of the sternum.

waist of the heart was present in the second and third intercostal spaces on the left. Auscultation revealed that in the second intercostal space to the right of the sternum there was a short, distinct systolic and a long, peculiarly purring diastolic murmur with musical pitch. A short systolic murmur was heard better over the apical area than at the base, and the diastolic murmur was less rough than the one heard over the upper portions of the chest. The heart rate was 84, there was sinus rhythm, with many premature beats. The blood pressure was 150 systolic and 50 diastolic. The liver was not enlarged. There was no edema. The Wassermann reaction was positive. Roentgenograms showed marked enlargement of the heart, with an oblique diameter of 18 cm. There was dilatation of the aortic loop.

The considerable increase in stroke volume and associated with it the powerful aspiration of venous blood during systole produce characteristic phenomena in the venous pulse. Usually in cases of aortic regurgitation there is a well marked systolic collapse of the jugular

veins. Also the abrupt emptying of the hepatic veins and the accompanying reduction in the volume of the liver occasionally produce a distinct systolic depression of the adjacent thoracic wall. If when palpating the liver one feels a jerky systolic depression of ribs and soft tissues, more easily recognized when the patient is holding his breath, one is justified in suspecting the presence of aortic regurgitation.

Ortner has pointed out that the systolic depression of the thoracic wall, provided it has existed at all, will disappear when cardiac failure with congestion sets in. This is due to the inadequate ventricular systole, whereby the aspiratory effect on the thoracic wall as well as on the column of venous blood is diminished, resulting in diminution or disappearance of the systolic collapse of the liver. A similar effect is noted with the appearance of auricular fibrillation. Occasionally a change in the type of hepatic pulsations is noted in the same patient, depending on compensation or failure and also on disturbances in the cardiac rhythm.

SUMMARY

A diffuse systolic depression of the anterior wall of the chest is found in instances of aortic regurgitation. This is a result of the increased stroke volume of the left ventricle, unless the aspiratory effect, owing to reduction of the ventricular volume during the systolic efflux, is neutralized by the opposing forces due to the systolic change in shape of the heart. In other instances there is no movement of the thoracic wall adjacent to the liver, while a distinct systolic depression is noted over the precordium. The diastolic pulsation of the thoracic wall in aortic insufficiency takes place slowly, as contrasted with the speed noted in the majority of cases of adhesive pericardial disease or tricuspid regurgitation in which an abrupt propulsion of the thoracic wall is noted during diastole.

PULSATIONS OF THE WALL OF THE CHEST

III PULSATIONS ASSOCIATED WITH TRICUSPID REGURGITATION

WILHELM DRESSLER, M D

VIENNA, AUSTRIA

The pulsatory features in the presence of tricuspid regurgitation often show a surprising similarity to those accompanying adhesive pericardial disease, and for this reason there is not infrequently confusion as to the proper diagnosis. Sometimes there is a widespread systolic depression of the wall of the chest in cases of tricuspid regurgitation which now and then markedly exceeds the actual cardiac area. The mechanism of this pulsation, as Lang¹ has shown, is essentially different from that of the pulsation noted in cases of adhesive pericardial disease. When there is tricuspid regurgitation, the right ventricle is usually enormously enlarged and is in wide contact with the ventral wall of the chest. During systole the right ventricle empties only a small amount of blood into the pulmonary artery, the larger amount flows in the direction of lesser resistance, i e, into the right auricle and hence into the large veins, primarily those of the liver. Thus during every systole there is an unusually marked diminution in the size of the right ventricle, recognized fluoroscopically by the wide marginal excursions of the heart, whereby the ventral wall of the chest, the ribs and the soft tissues are drawn inward. Besides this direct suction, there is an indirect aspiratory action on the thoracic wall. The blood discharged from the right ventricle does not remain in the thoracic cavity, as it does under normal conditions, but for the most part reaches the liver. This results in a rapid fall in the intrathoracic pressure and in an aspiratory action on the thoracic wall. The systolic aspiratory action on the thoracic wall is marked in cases of tricuspid regurgitation for the following reason. A rapid compensation for the fall in intrathoracic pressure by influx of venous blood is impossible because of regurgitation into the veins. Hence, the highest degree of systolic depression of the thoracic wall is often observed in association with tricuspid regurgitation. Commonly this depression is most strongly marked on the lateral portion of the left half of the wall, but other more distant portions also are affected by the indirect aspiratory action. The roentgen-

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From the *Heizstation*, Dr Hans Horst Meyer and Dr Emil Zak, directors

1 Lang, G. Ueber einige durch die Herzaktion verursachte Bewegungen der Brustwand und des Epigastriums, *Deutsches Arch f klin Med* **108** 35 1912

ologic examination reveals an abnormally large amplitude at the left side of the silhouette which is actually formed by the right ventricle

Furthermore, the characteristic pulsations of the ventral wall of the chest in the presence of tricuspid regurgitation are much influenced by regurgitation of blood into the liver. Most of the blood from the right auricle is diverted to the enlarged right lobe of the liver. Hence the adjacent sections of the thoracic wall are subjected to a strong thrust directed to the right and outward. This pulsation, together with the systolic depression of the left half of the chest, which likewise is chiefly directed to the right, leads to an abrupt systolic shift of the entire chest from left to right. This pulsation is extraordinarily characteristic of tricuspid regurgitation but is strongly marked only in certain cases. Volhard² expressed the opinion that the systolic propulsion to the right is occasioned by regurgitation of blood into the right auricle. This concept is incorrect, for careful palpation shows that the most marked expansion of the right wall of the chest does not occur at the level of the right auricle but farther caudad and outward, at the level of the strongly pulsating right lobe of the liver. If one places the right hand over the cardiac area and the left hand over the liver, one "can feel the blood being thrown back and forth between the hands, between the right ventricle and the liver" (Lang). Thus a characteristic seesaw movement results in cases of tricuspid regurgitation, Volhard called attention to this many years ago.

The systolic depression of the left wall of the chest cannot be observed in all cases of tricuspid regurgitation. It is absent whenever the centrifugal forces of the systolic change in shape of the heart are counteracting the aspiratory action due to the systolic diminution in cardiac volume, particularly in cases in which tricuspid regurgitation is associated with mitral stenosis. The depression is most marked when there is myopathy, associated with a higher degree of muscular tricuspid insufficiency, in which the propulsive forces of the systolic change in shape are usually less marked.

The venous blood, which is under high pressure at the beginning of diastole, flows with increased force toward the right side of the heart. It must be remembered that the flow of venous blood, which normally extends throughout almost the entire cardiac cycle, takes place in cases of tricuspid regurgitation only in the diastolic period. This explains the abrupt and unusually great increase in the volume of the right ventricle during diastole. Frequently it causes an equally rapid propulsion of the adjacent thoracic wall. Sometimes it may be referred to as the rapid diastolic propulsion of the thoracic wall, similar

2 Volhard, F. Ueber Leberpulse und über die Compensation der Klappenfehler, *Berl klin Wchnschr* 41 522, 1904

to that noted in cases of adhesive pericardial disease. As in obliterative pericarditis, there is heard a reduplicated apical second sound, produced by the rapid distention of the right ventricle at the beginning of diastole.

In a patient showing extreme tricuspid regurgitation the Broadbent sign was also observed, i. e., the systolic retraction of the lower ribs on the left dorsal aspect of the thoracic wall. In these cases the pulsation results from the extreme systolic aspiratory action which cannot be neutralized quickly enough by expansion of the atelectatic left side of the lung. Hence, not only the ventral wall of the chest but also the posterior dorsal portions of the left half of the chest are depressed by the atmospheric pressure. Broadbent's sign cannot, therefore, by any means be regarded as pathognomonic of adhesive pericardial disease. White³ has stated that he has observed this sign in a patient with a large heart without obliterative pericardial disease. I observed it once in a patient with aneurysmal dilatation of the left auricle in connection with mitral regurgitation.

It is rare to find isolated tricuspid regurgitation of endocarditic origin which presents the aforementioned pulsatory symptoms in such pure form. The characteristic pulsatory phenomena can be best studied in instances of muscular tricuspid insufficiency. In the following case these findings were present to an excessive degree.

H. A. was a man aged 58. In this case the postmortem diagnosis was relative tricuspid insufficiency, with excessive eccentric hypertrophy of the right ventricle. There was marked dilatation of the right ventricle as well as of the right auricle, the latter forming a sac almost the size of a fist. These two chambers formed the ventral wall of the heart, while the entire left ventricle faced the dorsal wall of the chest. The apical portion was formed by the right ventricle. The tricuspid orifice easily permitted the introduction of four fingers. The edge of the internal leaflet was drawn out and rolled in. The valves of all the orifices were without appreciable change. No etiologic factor could be found to explain the anomalous enlargement of the heart. The pericardial cavity was not obliterated.

When the patient was first examined there was marked cyanosis. No clubbing was noted. The legs showed slight edema. The veins of the neck were much enlarged. The external jugular veins were twice the size of a thumb. All other veins as far as visible were markedly dilated. The veins in the neck revealed an excessively marked regurgitation pulse which extended to the lobe of the ear, with each cardiac contraction there was noted not only a diffuse swelling of the neck but also a jerky movement of the head.

The cardiac area bulged but slightly. Inspection showed an abrupt movement of the whole chest from left to right simultaneous with the radial pulse and the ventricular hepatic pulse, it was therefore systolic. Careful observation revealed this pulsatory movement at the level of the shoulders. The pulsations consisted of two components. One was an inward movement (depression) of the inner and

3 White, P. D. *Heart Disease*, New York, The Macmillan Company, 1931.

4 The case has been described by Dr. R. Fischer, of the *Heizstation* (Wien klin Wchnschr **41** 657, 1928, **46** 1544, 1933).

particularly of the lateral portion of the left wall of the chest. The other component produced a definite though less prominent protrusion of the right side of the chest (fig 1). This pulsatory movement was more forceful in the caudal half of the chest, especially caudad to the sixth rib. On the left side the whole anterior and the lateral wall of the chest moved to the right and inward (dorsad) during systole (fig 2). This pulsation was slight near the clavicles and increased in intensity caudally. It was more marked between the left midclavicular and the anterior axillary line at the level of the sixth to the eighth rib, corresponding approximately to the apical portion of the heart (fig 3). An apical thrust could not be found (the postmortem examination showed that the apical portion was formed by the right ventricle and corresponded to the level of the upper aspect of the seventh rib, 2 fingerbreadths outside the midclavicular line). As the sternum was approached the component with the dorsal direction (depression) was less and less pronounced and was replaced by a movement which was almost exclusively frontal and directed to the right during systole. Near the left border of the sternum the type of pulsation changed so far as movement was observed, which was characteristic for the right half of the chest and which was directed to the

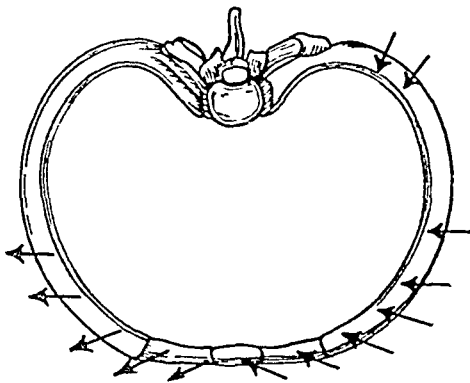


Fig 1 (patient H. A.)—The arrows indicate the direction of the movements of the thoracic wall observed during systole.

right and outward during systole. On the right side the greatest degree of propulsion was noted over the hepatic area, while from the sixth rib up to the clavicle a similarly directed, though much weaker, pulsatory movement was noted. The lateral borders of the chest on each side revealed a systolic shift to the right, this movement being much more pronounced on the left than on the right. The pulsatory propulsion in the region of the right auricle, i. e., in the parasternal area between the third and the sixth right rib, did not exceed the movements noted over the lateral areas of the same level. When the cardiac area was palpated with the right hand, while the left hand rested over the hepatic area, a definite seesaw movement was felt, with the right hand sinking in during systole and the left hand definitely elevated (fig 3). The left wall of the chest showed a marked systolic depression and a forceful, almost jerky propulsion at the beginning of diastole. The dorsal aspects of the left wall of the chest below the scapula showed a definite systolic depression which affected the soft tissues as well as the ribs (Broadbent's sign). The liver extended 4 fingerbreadths beyond the costal arch in the right midclavicular line, protruded above the level of the abdomen and revealed an exceedingly forceful systolic pulsation.

Percussion revealed that the cardiac dulness extended 4 fingerbreadths beyond the right sternal border. The lower third of the sternum showed absolute flatness. There was no undue flatness in the second and third intercostal spaces to the left of the sternum and over the upper portion of the sternum.

Auscultation gave surprisingly meager findings. The first sound at the apex was low and not quite pure. The second sound at the apex was definitely reduplicated, with the third accessory sound coinciding exactly with the movement of diastolic propulsion of the thoracic wall. The sounds at the base were hardly audible. No murmur was heard over the lower sternal area, nor was there any sound or murmur to the right of the sternum. The action of the heart was irregular, and auricular fibrillation was evident from the electrocardiogram. The heart rate was 76. The blood pressure was 135 systolic and 80 diastolic.

Roentgenograms revealed marked enlargement of the silhouette on each side, the transverse diameter being 20.5 cm. A wide pulsatory amplitude was noted along the whole left cardiac border, particularly near the base, decreasing in size toward the apical portion. The amplitude on the right was much smaller, and a definite inward movement was noted during systole which was well pronounced.

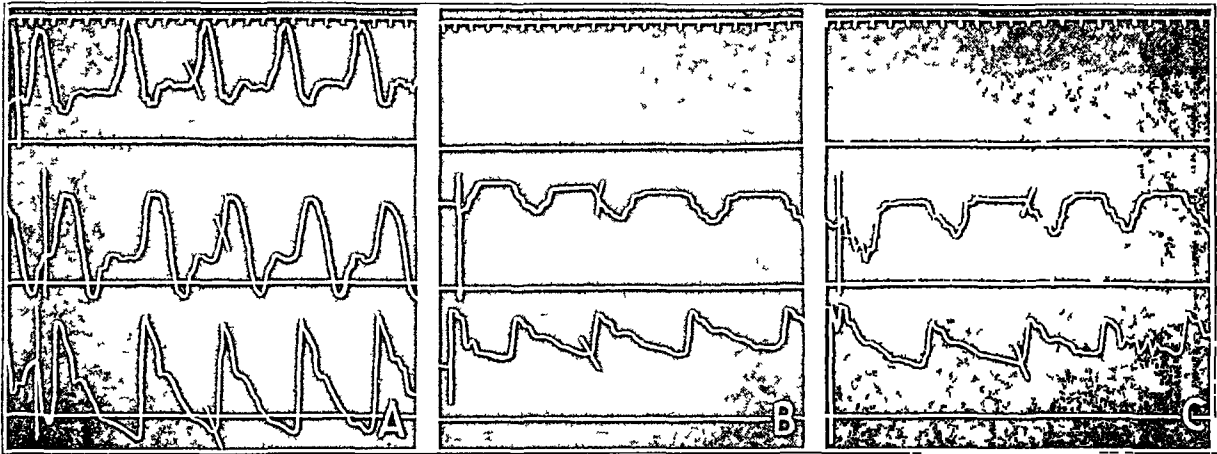


Fig 2 (patient H A)—The graphs demonstrate the systolic depression of the left side of the chest, the venous and hepatic pulse, in the presence of tricuspid regurgitation. A, the lower graph is for the radial artery, the middle graph, for the jugular vein, and the upper graph, for the liver. B, the lower graph is for the radial artery, and the middle graph, for the left parasternal line at the second intercostal space. C, the lower graph is for the radial artery, and the middle graph, for the left parasternal line at the fourth intercostal space.

near the diaphragm. The left leaf of the diaphragm showed a well marked systolic upward shift, while this pulsation was definitely smaller along the right leaf. There was marked dilatation of the superior vena cava, with but small pulsations. The aortic knob revealed a small amplitude, this finding was in marked contrast to the wide amplitude of the left cardiac border, proving that the latter was formed not by the left but by the right ventricle. Oblique views revealed no enlargement of the left auricle. The hilar vessels were not congested, the pulmonary fields showed increased transparency.

The fluoroscopic examination was particularly instructive regarding the pulsations of the thoracic wall. The excessive degree of systolic diminution of the right ventricle which formed the left cardiac contour was expressed by the unusually large amplitude and also by the forceful systolic upward shift (aspiration).

of the left diaphragmatic leaf, while the right diaphragmatic leaf revealed only a systolic upward shift of slight degree. The latter observation is explained by the fact that the right lobe of the liver, which was exceedingly large because of stasis, pulled on the right diaphragm like heavy ballast and prevented it from following the intrathoracic aspiratory force, while the movement of the left diaphragm, inhibited but slightly by the smaller left lobe of the liver, received a forceful pull from the direct aspiration of the caudal cardiac facies.

Isolated or predominant tricuspid regurgitation reveals a diffuse depression of the cardiac area but no apical thrust, provided the apical portion is formed by the enlarged right ventricle. The circumscribed apical thrust due to an increased activity of the left ventricle, in combination with a lesion of the aortic valve or mitral regurgitation, as a rule will be the less marked the more the tricuspid regurgitation prevails. Volhard and Lang accounted for this finding by assuming that the left ventricle is displaced by the enlarged right ventricle. There is

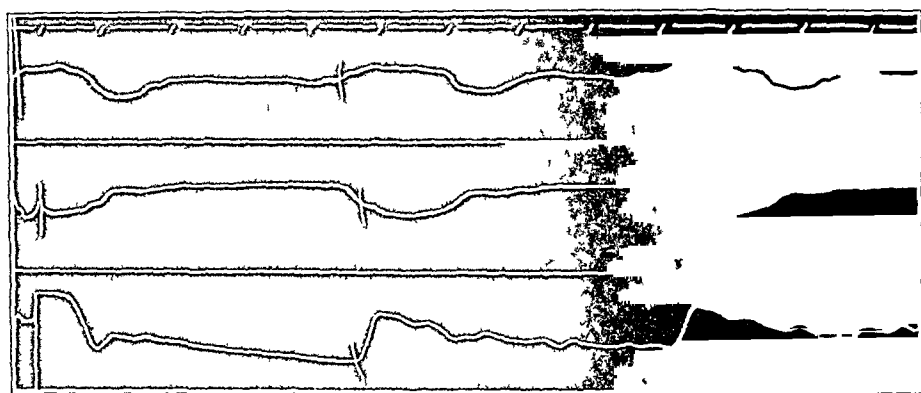


Fig 3 (patient H. A.)—The graph demonstrates the oppositely directed movement of the right and left sides of the chest, respectively, (seesaw movement) in the presence of tricuspid regurgitation. The lower graph is for the radial artery, the middle graph, for the sixth intercostal space, 4 cm. outside the left mid-clavicular line, and the upper graph, for the midaxillary line on the right side over the seventh rib.

also another factor, i. e., the inadequate filling of the left side of the heart, for during systole the greater quantity of blood regurgitates from the right side of the heart into the veins and a comparatively scanty amount of blood flows through the lesser circulation. This is explained roentgenologically by the marked transparency of the pulmonary fields.

Tricuspid regurgitation, either endocarditic or muscular in origin, and adhesive pericardial disease have important signs in common—the diffuse systolic depression of the precordium, sometimes also a diastolic propulsion of the thoracic wall, occasionally one finds the reduplicated second sound described by Friedrich. Ignorance of these conditions frequently leads to diagnostic errors. Tricuspid regurgitation is con-

tused with obliterative pericardial disease, and indications for surgical intervention are established. For instance, the Viennese surgeon Ewald reported the case of a woman aged 33 who showed signs of cardiac failure following articular rheumatism and a widespread systolic depression of the precordium. A well known clinician assumed this to be obliterative pericardial disease and sent her to the surgeon for cardiolysis. At operation, however, the pleura and pericardium were observed to be delicate and transparent. The patient died as a result of the operation, and necropsy revealed a lesion of the mitral valve, together with organic tricuspid regurgitation.

Systolic depression of the thoracic wall is especially frequent in cases of myopathy with muscular tricuspid insufficiency. Here the erroneous assumption of obliterative pericardial disease has even led to a new indication for Brauer's operation. It was found that resection of the ribs, made as the result of an erroneous interpretation of the indications, was followed by an improvement in the condition of the patient. Hence, Brauer's operation has been recommended by certain French authors (Lenormant and d'Aubigné⁵ and Worms and d'Aubigné⁶) in cases of enlargement of the heart with systolic depression of the thoracic wall, though they did not recognize that the accompanying tricuspid regurgitation was the cause of the pulsation of the wall.

In order to avoid confusing tricuspid regurgitation with obliterative pericardial disease the hand should be placed over the hepatic area in every case in which systolic depression of the precordium is noted. The characteristic strong systolic propulsion of tricuspid regurgitation is easily recognized.

SUMMARY

As in cases of aortic regurgitation, one finds in many instances of tricuspid regurgitation a diffuse systolic depression of the precordium. This is caused by the complete emptying of the right ventricle.

The aspiratory effect on the thoracic wall due to the reduction of the ventricular volume during the systolic efflux is particularly pronounced in tricuspid regurgitation, since the dilated right ventricle empties during systole in two directions simultaneously. In addition, the most important factor for the neutralization of the systolic fall of the intrathoracic pressure, i. e., the influx of venous blood, is eliminated by regurgitation into the veins. Regurgitation into the liver leads to a forceful propulsion of the right upper and lower portions of the

5 Lenormant, C., and d'Aubigné, R. M. La thoracectomie précordiale dans les symphyse et certaines hypertrophies cardiaques, *J de chir* **31** 161, 1928.

6 Worms, R., and d'Aubigné, R. M. Une observation de thoracectomie précordiale pour symphyse du péricarde, *Bull Soc de pediat de Paris* **26** 219, 1928.

chest and occasionally also to a jerky shift of the whole chest from left to right, the latter finding is particularly characteristic of this type of valvular lesion. The propulsion of the right side of the chest in association with the systolic depression over the cardiac area results in a seesaw movement, which Volhard was the first to describe for tricuspid regurgitation. No significance should be attributed to the systolic filling of the right auricle in the etiology of this pulsatory phenomena.

In contrast to aortic regurgitation, the apical thrust is absent as a rule in cases of tricuspid regurgitation. This is due to the fact that the left ventricle is poorly filled and is pushed away from the anterior wall of the chest by the much enlarged right ventricle. There is forceful filling of the right ventricle because of the high venous pressure, and occasionally one finds an abrupt diastolic pulsation of the thoracic wall, very similar to the diastolic cardiac thrust in the presence of adhesive pericardial disease. Likewise, Friedreich's reduplicated sound is occasionally heard. Confusion of tricuspid regurgitation with adhesive pericardial disease is therefore not uncommon, and only a careful observation of the forceful hepatic regurgitation pulse will insure against diagnostic error.

The systolic depression is often inhibited in the presence of a combination of tricuspid regurgitation with mitral stenosis, because of the opposing force of the change in shape of the heart.

EFFECTS OF A VITAMIN B₁ CONCENTRATE

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AND

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CHICAGO

EFFECT ON PERISTALSIS

Controversial opinions have been expressed as to whether vitamin B₁ deficiency occurs to any appreciable extent in otherwise healthy persons under the conditions of dietary habits prevailing in the United States¹ It is evident that a more or less pronounced deficiency may develop as a result of drastic voluntary dietary restrictions or in pathologic conditions associated with inanition, impaired utilization of food or consumption of food poor in vitamin B₁, e g, gastric ulcer, chronic ulcerative colitis, colectomy or pernicious vomiting of pregnancy Recognition of the deficiency is difficult, owing to the paucity of clinical symptoms Beriberi is known to have developed in a patient with a short-circuited small intestine² and in patients with other lesions responsible for gastro-intestinal disorders³ A lack of vitamin B₁ causes an impairment of digestive secretions and of oxidation of carbohydrates, it also lowers the tone of the gastro-intestinal musculature and causes anorexia Hence, a deficiency of vitamin B₁ may aggravate the intes-

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The vitamin B₁ concentrate employed was supplied by Eli Lilly & Co One cubic centimeter represents 150 Sherman-Chase units of vitamin B₁ The concentrate has not been offered for sale and was supplied exclusively for experimental purposes

1 Cowgill, G R Vitamin B₁ in Relation to the Clinic, J A M A **98** 2282 (June 25) 1932 Alvarez, W C Opinions of Four Hundred and Seventy Physicians in Regard to Advantages and Disadvantages of Using Bran and Roughage, Minnesota Med **14** 296, 1931 Harris, L J The Significance of Vitamins in Practical Experience, Brit M J **2** 367 (Aug 26) 1933 Clausen, S W The Influence of Nutrition upon Resistance to Infections, Physiol Rev **14** 309, 1934

2 Urmey, T V, Ragle, B H, Allen, A W, and Jones, C M Beriberi Secondary to Short-Circuited Small Intestine, New England J Med **210** 251 (Feb 1) 1934

3 Goudsmit, J Deficiency Symptoms in Chronic Gastro-Intestinal Diseases, Nederl tijdschr v geneesk **78** 3123 (July 7) 1934 Riesman, D, and Davidson, H S Beriberi Following Drastic Voluntary Dietary Restriction, J A M A **102** 2000 (June 16) 1934 Larimore, J W Chronic Ulcerative Colitis, ibid **90** 841 (March 17) 1928

tinal atony accompanying threatened or incipient paralytic ileus, a frequent aftermath of major operation, particularly laparotomy. Consequently, the deduction is justified that administration of vitamin B₁ in certain surgical conditions may be of therapeutic value, especially because a deficiency may lower the patient's resistance to infection. The desirability of administering vitamin B₁ in these conditions is enhanced by the observation that vitamin B₁ is not stored in the body and therefore a continuous optimal intake is necessary.

The difficulty of obtaining an absolutely pure product was not considered as a discouraging factor, because valuable information concerning the physiologic importance of many substances has been gathered before the completion of knowledge concerning their chemical identities.

METHOD

In the first series of experiments ileostomy was performed on eight dogs of both sexes, and peristalsis was recorded by the balloon-tambour method, a finger-cot being used as a balloon. Ileostomy was chosen in preference to a Thiry-Vella fistula, as it was considered a more physiologic method. The balloon was inflated with air, and a hydrostatic pressure of from 12 to 15 cm. was maintained in it. The balloon was inserted in the cephalad direction, precautions being taken not to have it expelled by the propulsive motions of the gut. Introduction of the balloon into the efferent loop may lead to failure to register intestinal movements, owing to a disproportion between the diameter of the balloon and the size of the cecum into which it may inadvertently be pushed. The peristalsis was recorded ordinarily for twenty minutes before and for from forty-five to sixty minutes after the injection of varying amounts of the concentrate. Concomitant respiratory tracings were made.

In the majority of the experiments a pronounced effect of the vitamin B₁ concentrate was noticed. The minimum effective dose was calculated to be approximately 0.7 cc. of the concentrate per kilogram of body weight if injected intravenously. In some instances the increase in tone was especially marked, in others the frequency and the amplitude of movements increased, while occasionally rhythmic contractions appeared. A combination of these results also was sometimes observed. The most conspicuous effect lasted on an average from three to ten minutes. Repeated injections on successive days were usually followed by identical reactions. Individual differences in the response of peristalsis to vitamin B₁ in various animals were noticed. Hypodermic injections were followed by less pronounced stimulation.

For the sake of comparison, the effects of several other substances on intestinal peristalsis were studied in the same animals. Ergotamine tartrate, pitressin and small doses of the dimethylcarbamate ester of *m*-oxyphenyltrimethylammonium-methylsulfate (prostigmin) had no noticeable effect, while physostigmine and acetylbetamethylcholine (mecamylol) produced, with the dose employed, increase of tonus, frequency and amplitude of contractions comparable to, but less pronounced than, those caused by the vitamin B₁ concentrate.

A crystalline product of vitamin B₁⁴ was tested on two dogs. The results obtained were identical with those obtained with the vitamin B₁ concentrate. A

⁴ This crystalline product of vitamin B₁ was supplied by Merck & Co., Inc.

subcutaneous injection of 10 mg of atropine did not inhibit the stimulating effect of an intravenous injection of 7 cc of vitamin B₁ concentrate given ten minutes later

In another series of experiments varying doses of the vitamin B₁ concentrate were added to Ringer's solution in which a segment of small intestine of a guinea-pig was immersed. The resulting spastic contraction was sometimes followed by an increase in the frequency and amplitude of the peristaltic movement. In several instances peristalsis became erratic.

EFFECT ON BLOOD PRESSURE

Muscular weakness and lassitude of dogs after intravenous injections of large doses of vitamin B₁ suggested a systemic effect. Therefore, a study of the effect of vitamin B₁ on the blood pressure was undertaken. The pressure was recorded by means of a cannula introduced into the carotid artery. A pronounced and abrupt fall in blood pressure was observed in every instance in dogs and rabbits. The effect of the crystalline product also was tested. In one experiment no effect was noticed, while in another a slight fall in blood pressure was recorded. A rapid return to the normal height was usually observed a few minutes after the injection of the vitamin B₁ concentrate. An injection of 0.25 cc of a 1:1,000 solution of epinephrine preceding an intravenous injection of 2 cc of the vitamin B₁ concentrate did not prevent a sharp drop in blood pressure. The fall in blood pressure was slight after the subcutaneous injection of the vitamin B₁ concentrate.

Attempts were made to identify the substance responsible for the depressor effect of the vitamin B₁ concentrate on the blood pressure. Barsoum and Gaddum⁵ made the observation that the presence of histamine in the bath renders a strip of rectal cecum of a fowl insensitive to doses of histamine sixty times as large as those which had previously caused contraction. These facts can be made the basis of a method of identification of active substances in tissue extracts. Similar experiments were performed with a strip of the small intestine of a guinea-pig and on the proximal portion of the rectal cecum of a chicken. When 0.00000004 cc of the vitamin B₁ concentrate in 1 cc of Ringer's solution was given a steep rise in the tonus and an increase in the amplitude of the contractions were produced. After this effect had subsided, the same dose of histamine had no effect, pointing to the presence of histamine in the vitamin B₁ concentrate.

Major⁶ has stated that histamine produces a rise in the blood pressure of atropinized rabbits, while choline has no effect. According

5 Barsoum, G. S., and Gaddum, J. H. The Pharmacological Estimation of Adenosine and Histamine in Blood, *J. Physiol.* **85** 1 (Aug. 22) 1935.

6 Major, R. H., and Weber, C. J. Observations on the Depressor Substances in Certain Tissue Extracts, *J. Pharmacol. & Exper. Therap.* **37** 367 (Nov.) 1929.

to Vincent,⁷ choline causes a fall in blood pressure in etherized rabbits, while histamine has no effect or produces a rise, in atropinized rabbits, according to this author, choline causes a marked rise in blood pressure, while histamine has no effect or is followed by a rise in pressure. The rise in pressure in etherized rabbits after the intravenous injection of the vitamin B₁ concentrate and the absence of an effect in an atropinized rabbit apparently demonstrated the presence of choline in the concentrate, while no conclusion could be reached as to the presence of histamine.

These depressor substances may be undesirable under many circumstances. Therefore, the company which supplied the product made further attempts to purify it. The intravenous injection of a 2 cc of a new lot of vitamin B₁ concentrate produced a slight drop in blood pressure in a dog. An attempt was made to reproduce the same degree of fall in blood pressure with histamine. For this purpose, 0.0005 mg was required. In other words, the effect of 1 cc of the new concentrate corresponded to the effect of 0.00025 mg of histamine. In an etherized rabbit 0.2 mg of histamine produced a slight rise in the blood pressure. After the subcutaneous injection of 2 mg of atropine the same dose of histamine caused a slight rise, followed by a marked fall in pressure and death of the animal. After this preliminary experiment 2 cc of the new concentrate was injected intravenously into an etherized rabbit. A slight fall in blood pressure followed. Fifteen minutes after the subcutaneous administration of the same amount of atropine, 2 cc of the vitamin B₁ concentrate had no effect on the blood pressure. One milligram of histamine produced a sharp drop in pressure. The results of these experiments point to the presence of choline and the absence of an amount of histamine capable of producing a rise in pressure.

The effect of the new concentrate on intestinal contractions was studied on a strip of small intestine from a guinea-pig. It was found that 0.025 cc of the concentrate per cubic centimeter of Ringer's solution had no effect, while 0.0005 mg of histamine produced a spastic contraction. In other words, 1 cc of the new concentrate contained less than 0.2 mg of histamine. In another series of experiments a strip of rabbit intestine was used. Gradually increasing doses of the new lot were employed, starting with 0.00000001 cc. It was found that 0.04 cc of concentrate per cubic centimeter of Ringer's solution caused a lowering of the amplitude of the intestinal contractions, 0.00002 mg of histamine had no effect, while 0.01 mg was responsible for a rise in the amplitude of the contractions. The contractions became

⁷ Vincent, S., and Curtis, F. R. Nature of Depressor Substance or Substances in Tissue Extracts, *Lancet* 1 1142 (June 12) 1926.

still larger after the addition of 0.1 mg of histamine. In other words, in these experiments no detectable amount of histamine could be found in the new concentrate.

COMMENT

The old vitamin B₁ concentrate exerted a stimulating effect on the tonus of the small intestines of dogs and on the frequency and amplitude of peristaltic movements. It also produced a sharp drop in blood pressure in dogs and rabbits. In one experiment a slight fall in blood pressure was observed after the injection of a crystalline product. This observation suggests that the effect was possibly not due wholly to impurities. The concentrate apparently contained histamine and choline. The presence of these depressor substances is not necessarily an undesirable feature, because the field of usefulness of histamine and related substances is gradually becoming wider. For instance, they are recommended in the treatment of rheumatic conditions, peptic ulcers and certain vascular lesions. However, it seems that they should be avoided in many conditions, particularly those associated with low blood pressure. Hence, the attempt was made to eliminate the depressor substances from the concentrate. The new batch apparently contained extremely small doses of histamine and probably also choline, but there was no stimulating effect on intestinal contractions. The comparison of the effect of the old and that of the new batch suggests that in the process of purification the elimination of depressor substances deprived the concentrate of the effect of peristalsis. A conclusion is allowed that the stimulating effect of the old batch on intestinal contractions was due to the presence of histamine and possibly also of choline. If this assumption holds true, it remains a matter of conjecture whether or not the intestinal atony characteristic of vitamin B₁ deficiency is a direct result of a lack of vitamin B₁ and not of histamine and choline. Further investigations must show whether B₁ avitaminosis is accompanied with a diminution in the amount of histamine and choline in the body. The genesis and mechanism of a lack of these substances remain obscure.

The knowledge of the presence of depressor factors in vitamin B₁ concentrates is of great importance, as it helps to outline the indications and contraindications for the use of these products. It also points the direction in which the further process of purification of vitamin B₁ concentrate must go. Cowgill⁸ has justly stated that recent perfection of methods for preparing vitamin B₁ concentrate suitable for injections should lead to more extensive trial of this type of therapy.

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⁸ Cowgill, G. R. *The Vitamin B Requirement of Man*, New Haven, Yale University Press, 1934, p. 20.

TRACTION DIVERTICULUM OF THE ESOPHAGUS

ROENTGENOGRAPHIC DEMONSTRATION, SYMPTOMS NOTED IN A SERIES OF TWENTY-SIX PATIENTS

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Traction diverticulum of the esophagus, noted with relative frequency in adults at necropsy¹ and demonstrable to some degree roentgenographically² has been generally thought to be without symptoms and of minor clinical importance³. Among ten patients reported on in 1932² and among sixteen additional patients in whom the condition was discovered under the conditions and method outlined in that report, symptoms recurred with such frequency as to cast doubt on the theory of absence of symptoms with this lesion.

This paper will present an analysis of the symptomatology and certain findings in twenty-six cases of traction diverticulum situated in the midthird of the thoracic portion of the esophagus, in close proximity to the bifurcation of the trachea and to the hilus of the left lung.

ANALYSIS OF COMPLAINTS

Symptoms were attributed to the diverticulum by ten (38.5 per cent) of the twenty-six patients. In eight cases these symptoms were the patient's chief complaint, while in the remaining two cases (that of a

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1 Starck, H. Die Divertikel der Speiseröhre, Leipzig, F. C. W. Vogel, 1900.
Heinen, W. Ein Beitrag zur Kenntnis der an der Bifurkation der Trachea gelegenen Divertikel des Oesophagus, Frankfurt Ztschr. f. Path. **1** 176-186, 1907.
Kragh, J. Diverticules tuberculeux, dits diverticules de traction, l'oesophage d'un boeuf, Compt. rend. Soc. de biol. **85** 755-757, 1921.

2 Sturtevant, M., Shapiro, L. L., and Wallace, R. P. Traction Diverticulum of the Esophagus, Am. J. Roentgenol. **27** 187-192 (Feb.) 1932.

3 Barrett, N. R. Diverticula of the Thoracic Esophagus, Lancet **1** 1009-1011 (May 13) 1933.
Heacock, C. H. Diverticula of the Thoracic Portion of the Esophagus, South. M. J. **23** 517-520 (June) 1930.
Hill, W. Pharyngeal and Esophageal Diverticula, Brit. M. J. **2** 1163-1169 (Dec. 18) 1926.
Lahey, F. H. Surgical Management of Pharyngo-Oesophageal Diverticulum, Surg., Gynec. & Obst. **51** 227-236 (Aug.) 1930.
Carmen, R. D. The Roentgen Diagnosis of Diseases of the Alimentary Canal, ed. 2, Philadelphia, W. B. Saunders Company, 1921.
Vinson, P. P. Diverticula of the Thoracic Portion of the Esophagus, Arch. Otolaryng. **19** 508-513 (April) 1934.

man with cardiac disease and that of a destitute, undernourished woman during the menopause) esophageal symptoms were of secondary importance. Three of the ten patients had had continuous symptoms, in three the symptoms showed periodicity, while the remaining four were seen soon after the onset of their symptoms.

Pain behind the sternum was felt by six patients. A sensation of weight or heaviness was complained of by four and burning by three, while sudden, sharp, short, sticking, dull, constant, choking and constricting were the terms used once each to describe the discomfort. Occasionally food would increase the pain, but this was neither a frequent nor a constant finding. The intensity of the pain varied from mild to severe and bore no relationship to position of the body, respiration or time of day. Usually the pain was referred to the midsternum, but when severe it was not localized and was described as in the chest. Four patients experienced radiation of the pain, by two it was referred laterally to the ribs below the axilla and by two to the interscapular region.

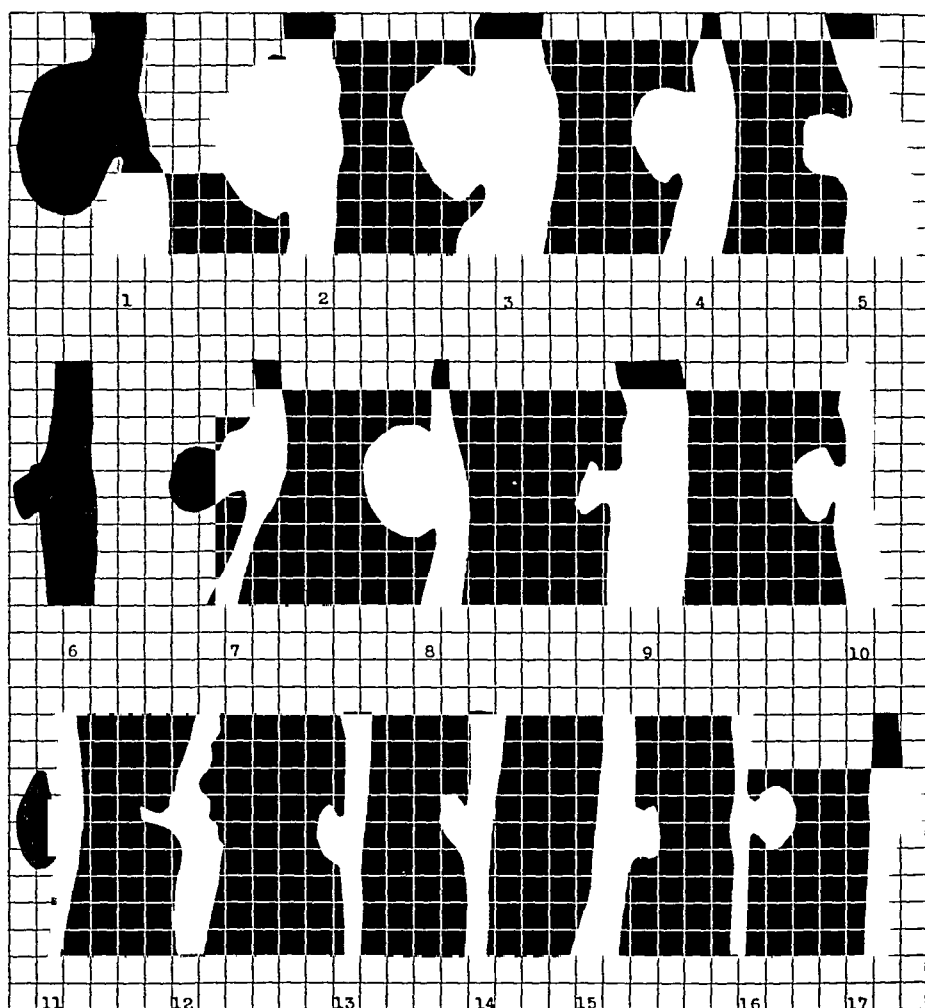
Dysphagia, distinct from substernal pain, was experienced by six patients. Swallowing was not only difficult but painful. Descriptive terms used were discomfort, pain, sticking, heaviness and soreness. The degree of dysphagia varied from mild to severe, with necessary restriction of the diet to liquids and soft foods.

Hematemesis occurred in three cases, and in two it was the only complaint. In two the loss of blood was moderate and was described as small and as a cupful, respectively. In these two cases regurgitation was spontaneous and unassociated with nausea or retching. The third patient on two occasions had a copious hemorrhage, which was estimated at more than a pint (500 cc), of bright red blood, containing some coffee-ground material. Immediately after the hemorrhage he felt weak and faint. The erythrocyte count fell to 3,500,000, with a hemoglobin (Sahli) content of 45 per cent. In 2 cases there was melena after the hemorrhage.

Other symptoms of minor importance and infrequent occurrence were eructations, simple vomiting, hiccup, pain high in the epigastrium and weakness.

An attempt was made to ascertain whether other findings of this series were in any way related to the causation of symptoms. The average age of the patients who showed symptoms was 53.7 years, the symptomless patients were on an average of 4 years older than those with symptoms. There were two and one-half times more men than women in each group, and this approximated the sex relationship of all patients examined. A single diverticulum was present in each case in which there were no symptoms and, except in two cases in which there

were multiple pouches, in all the cases in which there were symptoms. In the cases of symptomless diverticulum the long axis of the sac was directed to the left obliquely (anteriorly and to the left) in thirteen and to the right obliquely in three. In four of the cases in which there were symptoms the direction was to the left obliquely and in six cases to the right obliquely. This predominance of direction of the sac to the



Exact tracings of the diverticula on centimeter graph paper from the roentgenograms made with a tube-film distance of 30 inches (75 cm). Symptomless diverticula 1, 2, 5, 6, 8, 9, 10, 13, 14 and 17, mild symptoms, 4, 7, 11 and 16, severe symptoms, 3, 12 and 15.

right obliquely in those patients with symptoms is unexplained. No definite relationship between the size of the sac and the occurrence of symptoms could be established. Several of the smallest sacs were noted in patients with the most severe symptoms, and a number of the largest sacs produced no symptoms whatever (figure).

SUMMARY

Substeinal distress, dysphagia or hemorrhage, either alone or in combination, occurred in the ten cases of traction diverticulum associated with symptoms. In a few the symptoms were chronically present, but in the majority a period of comfort separated the attacks.

CONCLUSION

Evidence is presented to show that traction diverticulum of the esophagus caused symptoms in slightly more than a third of a small series in which diagnosis was established during life roentgenographically.

LEUKEMIA WITHOUT LEUKOCYTOSIS (ALEUKEMIC MYELOSIS) AND WITHOUT SPLENOMEGALY

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It is well known that leukemia may occur without leukocytosis. In such cases the clinical picture of weakness and pallor and the varying degrees of lymphadenopathy, splenomegaly and hepatomegaly, with the blood picture of anemia and thrombopenia and the presence of myeloblasts in the stained blood film, make the diagnosis possible. The anatomic findings in the cases hitherto reported¹ show a similarity to the anatomic picture in true leukemia. There is, however, relatively little to be found in the medical literature on the occurrence of leukemia without splenomegaly. In a recent review² on leukemia it was mentioned that there are instances in which no splenic enlargement is noted. Hirschfeld³ reported four cases of leukemia without splenomegaly, Ordway and Gorham⁴ reported one case and Kracke and Garver⁵ also described one case. Recently Parkes Weber⁶ reported a case of aleukemic myelosis without splenic enlargement in which the condition

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4 Ordway, T., and Gorham, W. The Diagnosis and Treatment of Diseases of the Blood, in Christian, H. A. Oxford Monographs on Diagnosis and Treatment, London, Oxford University Press, 1930, vol. 9.

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clinically simulated aplastic anemia. He stated that many cases in which the clinical diagnosis was aplastic anemia have doubtless been examples of aleukemic myelosis.

During the past several years in the wards of the University of California Hospital there have been an unusual number of patients with leukopenia⁷ with an abnormal leukocyte picture, showing varied types of involvement and presenting difficult diagnostic problems. Among these was a group of patients with leukemia not associated with splenomegaly. Myeloid hyperplasia of the bone marrow consistent with leukemia was noted in all these cases. It is our purpose in this paper to present the histories of five of these patients, to classify the condition as leukemia without splenomegaly and without leukocytosis and to discuss the clinical recognition of this condition.

REPORT OF CASES

CASE 1—E. P., a white woman aged 21, was admitted to the University of California Hospital on Feb. 2, 1932, complaining of weakness, dyspnea, menorrhagia and bleeding gums. Nine months prior to the patient's entry into the hospital her illness began with an attack of nausea, vomiting, diarrhea and headache, accompanied with a temperature ranging between 99 and 100 F. After an examination her physicians told her that her hemoglobin value was 27 per cent, that she had leukopenia and that immature white blood cells were present in the stained film. She was given three transfusions, after which the symptoms subsided, and she was told that the hemoglobin value had increased. Two months later the symptoms recurred, and the hemoglobin value was reported to be 44 per cent. During the next six months the patient received transfusions at intervals of from two to three weeks. Within the week prior to entry into the hospital she was given three transfusions each of 500 cc of whole blood.

Physical Examination—The patient appeared well developed and well nourished. There was no evidence of infection in the skin, ears, nose or throat. The gums appeared swollen and spongy, and there was slight bleeding around the gingival margins, but signs of suppuration or active inflammation were not present. There were a few scattered fading areas of ecchymosis on the skin. Lymph nodes, averaging in size from 1 to 2 cm., were present in the anterior cervical triangles, and a few nodes were felt in the axillae, but none could be palpated in the epitrochlear or inguinal regions. The heart was not found to be enlarged on percussion, and no cardiac murmurs were audible on deep inspiration. The edge of the liver descended 2 cm. below the right costal margin, but the spleen could not be palpated.

Laboratory Data—The blood count showed erythrocytes, 4,310,000 per cubic millimeter, hemoglobin, 94 per cent (129 Gm.) Sahli, and leukocytes, 7,600 per cubic millimeter. The differential count showed segmented polymorphonuclear leukocytes, 39 per cent, nonsegmented leukocytes, 2 per cent, lymphocytes, 45 per cent, monocytes, 3 per cent, myelocytes, 4 per cent, myeloblasts, 5 per cent, and unclassified immature forms, 2 per cent. One nucleated red blood

⁷ Mettler, S. R., and Olsan, H. T. The Clinical Significance of Leucopenia with Special Reference to Idiopathic Neutropenia, *Ann Int Med* 6: 855, 1933.

cell was seen per hundred white blood cells. The number of platelets was greatly diminished. Cultures made of material from the stools failed to show any growth of pathogenic organisms.

Course of the Illness—Three days after the patient's admission to the hospital the leukocyte count was 4,600 per cubic millimeter. Examination of a stained film showed that 4 per cent of the cells were large and round, with basophilic cytoplasm and a nucleus which contained from 4 to 6 nucleoli. These cells were considered myeloblasts. On the same day a slight decrease in the erythrocyte count and hemoglobin content was noted. From this time on there was a progressive drop in the level of the erythrocytes and leukocytes. On February 25 the blood count showed hemoglobin, 50 per cent, erythrocytes, 1,780,000 per cubic millimeter, and white blood cells, 1,700 per cubic millimeter. The differential count showed segmented polymorphonuclear leukocytes, 44 per cent, nonsegmented leukocytes, 20 per cent, eosinophils, 2 per cent, lymphocytes, 16 per cent, monocytes, 2 per cent, myelocytes, 10 per cent, and myeloblasts, 6 per cent. One nucleated red blood cell was seen per hundred white blood cells. There was marked achromia of the red blood cells. A sparse number of platelets was noted.

At this time continuous oozing of blood from the gums and profuse menses had been present for a week. Administration of iron and ammonium citrates, 6 Gm daily, solution of potassium arsenite USP and roentgen irradiation over the long bones failed to alleviate the patient's symptoms. On February 26 and 29 the patient received transfusions, each of 500 cc of whole blood, which were followed by a slight increase in the number of erythrocytes and in the hemoglobin content with a slight lessening of bleeding. There was persistent leukopenia, with approximately 1,500 white blood cells per cubic millimeter. Three days prior to the patient's death the white blood cell count was 1,350 per cubic millimeter. The differential count was segmented polymorphonuclear leukocytes, 18 per cent, nonsegmented leukocytes, 23 per cent, eosinophils, 4 per cent, lymphocytes, 25 per cent, monocytes, 4 per cent, myelocytes, 18 per cent, myeloblasts, 6 per cent, and unclassified immature forms, 2 per cent. There were 2 nucleated red blood cells per hundred white blood cells. Anisocytosis and poikilocytosis were marked, and the number of platelets was greatly decreased.

About five days after the last transfusion there was evidence of hemorrhage from the bladder and gastro-intestinal tract. The patient died on March 6. During the five weeks she was under observation in the hospital the temperature varied from 36.8 C (98.2 F) in the mornings to as high as 37.4 C (99.3 F) in the afternoons.

Clinical Diagnosis—The clinical diagnosis was aleukemic myelosis with slight leukemic metaplasia of the cervical lymph nodes.

Biopsy of a Cervical Lymph Node—On February 6 a specimen from a cervical lymph node was removed for biopsy. The sections showed that the architecture of the lymph node had been largely replaced by tumor cells which varied somewhat in shape, size and character. Many of these cells appeared to be overgrown germinal centers and reticulum cells, but still more appeared to be of myeloid types. The latter cells had rather abundant and large indented nuclei, many of which showed mitosis. In addition there were many nucleated red blood cells, and the nuclei of these cells were seen in all stages of degeneration and fragmentation. In the vicinity of the myelocytic cells were many young polymorphonuclear leukocytes. Among the myelocytic cells there were neutrophilic and eosinophilic types. The cellular structure of the node was believed to be

consistent with the myeloid and erythroblastic metaplasia occurring in a myelogenous type of leukemia. The diagnosis was leukemic involvement of the lymph node.

Gross Postmortem Examination—The body appeared to be well developed and fairly well nourished. There was marked pallor of the skin and mucous membranes. In the skin over the forehead, cheeks, chest, abdomen, arms and legs there were numerous areas of petechial hemorrhage, measuring up to 3 mm in diameter. The gums were greatly swollen, spongy and bluish, and from them exuded a sanguineous fluid. Lymph nodes, averaging 1 cm in diameter, were present in the anterior cervical triangles, the axillae and the inguinal regions. The postmortem examination was limited. Through a suprapubic incision the abdominal viscera were examined. A specimen of bone marrow was obtained from the right femur.

Internal Organs There was no evidence of septic peritonitis. Many petechial hemorrhages were seen in the peritoneum. The edge of the liver projected 1 cm below the right costal margin.

Spleen The spleen weighed 190 Gm. The surface appeared smooth and glistening. Cut section showed that the pulp was slightly softer in consistency than normal but could not be readily scraped away on the edge of a knife. The size of the malpighian bodies appeared normal.

Pelvic Organs The pelvic organs were removed in toto. The bladder when opened contained a large blood clot, and the mucosa was covered with sanguineous material. The uterine cavity was filled with hemorrhagic fluid. There was no evidence of suppuration. The ovaries appeared to be of normal size, in one there was a cyst which contained recently clotted blood.

Lymph Nodes The mesenteric and retroperitoneal nodes were slightly enlarged. The largest one seen measured 0.5 cm in length. On cut section the tissue appeared firm and reddish pink.

Bone Marrow A specimen of bone marrow was removed from the upper third of the left femur. It appeared reddish gray and was of firm consistency.

Microscopic Postmortem Examination—The bone marrow was markedly cellular and made up of blood-formative cells and a slight amount of undifferentiated connective tissue. There were large numbers of myelocytes and myeloblasts forming a compact hyperplastic leukopoietic tissue. Only occasional small foci of erythropoiesis were noted.

Spleen The spleen showed a nearly normal preservation of architecture. The centers of the malpighian bodies were composed of large cells with pale eosinophilic cytoplasm and vesicular nuclei. In the sinusoidal spaces were small numbers of myeloid elements similar to those observed in the bone marrow. There were a few cells that resembled nucleated red blood cells.

Liver About the portal spaces in the parenchyma were small accumulations of abnormal cells. The cells were chiefly of a large mononuclear type, and an occasional cell contained a mitotic figure.

Lymph Node A section of a retroperitoneal lymph node showed slight alteration from its normal architecture. The follicles were smaller than normal. Scattered throughout the tissues between the lymphoid cells were young myeloid cells.

Postmortem Diagnosis—The diagnosis was aleukemic myelogenous leukemia, with leukemic bone marrow, moderate leukemic infiltration of the liver, slight myeloid metaplasia of the spleen and lymph nodes, and purpuric manifestations in the skin, bladder, uterus and gastro-intestinal tract.

Comment—The onset of this patient's illness was characterized by symptoms arising from the gastro-intestinal tract and associated with fever and leukopenia. After the patient was admitted to the hospital it was thought that the leukopenia might have been due to an abnormal response of the bone marrow to sepsis in the intestinal tract. Cultures of material obtained from the stools and blood failed to show pathogenic organisms. The diagnosis of aleukemic myelosis was suggested by the appearance of myeloblasts in the stained blood film and was substantiated by the myeloid metaplasia of the cervical lymph node removed for biopsy. Throughout the course of the illness the spleen was not enlarged. Pathologic observations essential for the diagnosis of aleukemic myelosis were made post mortem.

CASE 2—T. B., a white American man aged 38, entered the University of California Hospital on July 20, 1933. Eight months prior to entry he had an attack of fever and weakness, associated with muscle pain. His physician made the diagnosis of influenza. The patient was in bed one week, afterward he regained his strength slowly. During the winter he did not feel as well as formerly and continued to complain of weakness, aching of muscles and nausea but no vomiting. About one month before entry roentgenograms were taken of the gastro-intestinal tract, and a diagnosis of peptic ulcer was made. For the patient were prescribed rest in bed and a modified Sippy regimen, with milk feedings and alkaline powders. However, he continued to be weak. There was no history of blood in the stools or of diarrhea. Ten years previously the patient had pleurisy with effusion, after thoracentesis he recovered completely. There was no history of other infections.

Physical Examination—The patient appeared well developed and well nourished. There was marked pallor of the skin. The heart was not enlarged on percussion, its action was regular, but a soft, blowing systolic murmur was heard over the mitral and pulmonic regions. Neither the liver nor the spleen could be felt. There was no enlargement of the superficial lymph nodes. Slight pyorrhea alveolaris was noted, but there was no evidence of respiratory or genito-urinary infection.

Laboratory Data—The blood count on July 20 showed hemoglobin, 55 per cent (77 Gm.) Sahli, erythrocytes, 3,270,000, and leukocytes, 2,300. The differential count showed polymorphonuclear leukocytes, 7 per cent, nonsegmented leukocytes, 22 per cent, lymphocytes, 42 per cent, monocytes, 26 per cent, myelocytes, 1 per cent, and unclassified cells, 2 per cent. Two nucleated red blood cells were seen per hundred leukocytes in the stained film. The icterus index was 7.5. There were 34 per cent reticulocytes. The platelets were greatly reduced in number.

Course of the Illness—The patient remained under observation in the hospital for three weeks, during which time the anemia and the leukopenia persisted with only slight variation. There was no apparent hematopoietic reaction to liver extract given either parenterally or by mouth. The patient was discharged on August 10.

Because of failure to gain in strength, the patient returned to the hospital on August 28. On this occasion neither lymphadenopathy nor enlargement of the spleen was apparent. The blood count showed hemoglobin, 43 per cent (61 Gm.) Sahli, erythrocytes, 2,460,000 per cubic millimeter, leukocytes 2,450 per cubic millimeter and reticulocytes, 16 per cent. The differential count showed seg-

mented polymorphonuclear leukocytes, 2 per cent, nonsegmented leukocytes, 14 per cent, eosinophils, 1 per cent, lymphocytes, 28 per cent, monocytes, 14 per cent, myelocytes, 10 per cent, and promyelocytes and myeloblasts, 31 per cent. There was a slow and gradual decrease in the erythrocyte and leukocyte levels in spite of the use of the following therapeutic measures: liver extract, pent-nucleotide, roentgen irradiation over the long bones and transfusions of whole blood. The patient's temperature showed a daily fluctuation from 36.8 to 38.6 C (98.2 to 101.5 F). On October 24 hemorrhages appeared in the retinas. The blood count showed hemoglobin, 10 per cent (14 Gm) Sahli, erythrocytes, 500,000 per cubic millimeter, and leukocytes, 980 per cubic millimeter. The differential count showed segmented polymorphonuclear leukocytes, 8 per cent,

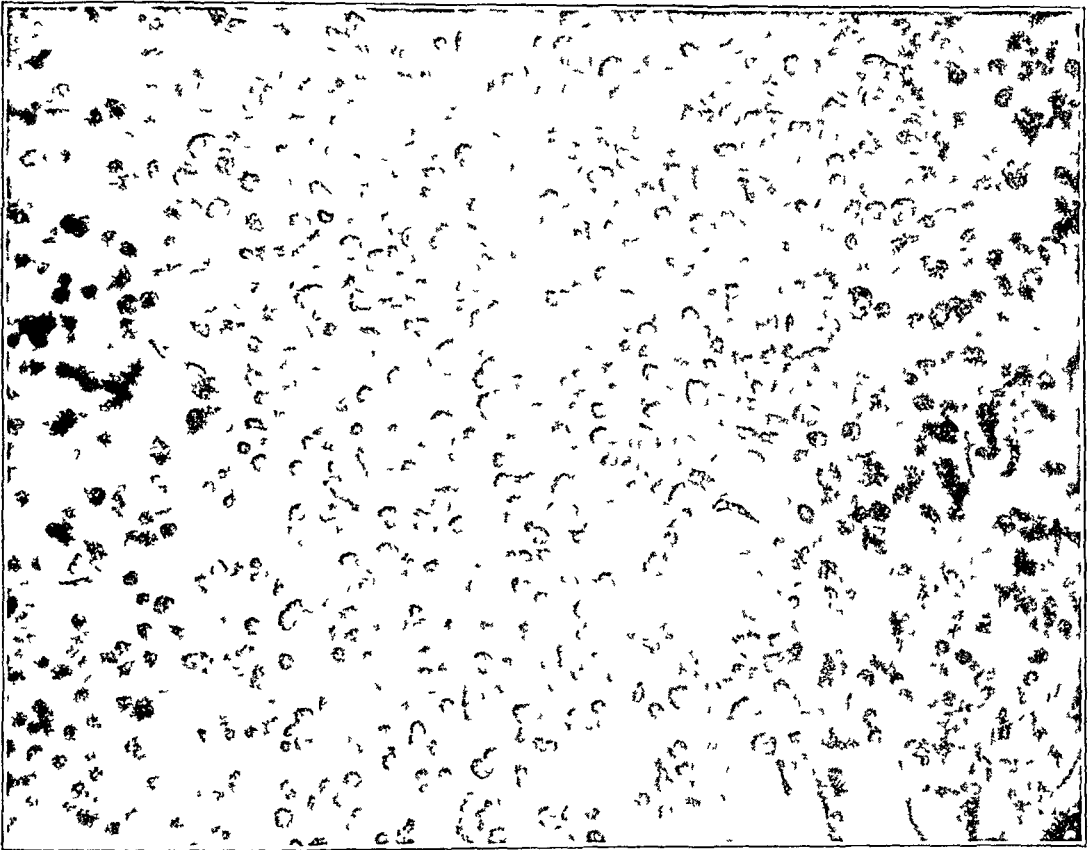


Fig 1 (case 2)—Photomicrograph of the marrow removed from the sternum for biopsy, $\times 300$. Note the increased cellularity.

nonsegmented leukocytes, 28 per cent, lymphocytes, 16 per cent, monocytes, 12 per cent, myelocytes, 20 per cent, and myeloblasts, 16 per cent. There were 40,000 platelets per cubic millimeter. At this time the tip of the spleen was barely palpable. Death occurred on October 27.

Clinical Diagnosis—The diagnosis was aleukemic myelosis, with anemia and thrombopenia.

Biopsy of Sternal Marrow—Sections of sternal marrow removed for biopsy showed hyperplasia but no fat. Groups of megakaryocytes were evident. The predominant type of cell had a large vesicular nucleus containing several chromatin masses and often darkly stained nucleoli. The outline of the cell was not distinct, the cytoplasm stained lightly and was light blue. Many of the cells

were in groups and appeared to be situated close to the endothelial cells of small capillaries. In an occasional cell relatively normal mitosis was present. A few eosinophilic myelocytes were to be seen. Small groups of erythroblasts and normoblasts could be distinguished, but they were not as predominant as the cells of the myeloid series. The diagnosis was hyperplasia of the bone marrow with increased myelopoiesis and erythropoiesis.

Gross Postmortem Examination—The autopsy was performed by Dr G Biskind. The body was that of a well developed, slightly undernourished man. There was no evidence of purpura in the skin. Dentition was normal, and the gums were not abnormal. No masses were palpable in the abdomen. No lymph nodes could be palpated in the neck, axillae or inguinal region.

Internal Organs There was no evidence of infection in the peritoneal cavity. The mesenteric lymph nodes were not enlarged, but there were a few large nodes around the head of the pancreas. The left pleural cavity was obliterated by old fibrous adhesions. There were no enlarged nodes in the mediastinum.

Heart The heart weighed 380 Gm. The endocardium showed tigroid mottling, but there was no evidence of an inflammatory process.

Lungs There was no evidence of any disease process.

Liver The liver was enlarged and weighed 2,270 Gm. On the surface, which was brown, there were small, discrete, scattered zones of gray cellularity. These were not numerous. On cut section a certain amount of terminal congestion was evidenced by the prominence of the hepatic veins and lobules. The parenchyma was brown and soft, owing to an increase in the amount of fat. Gray cellular zones were relatively infrequent and small. The gallbladder was small, and pressure on it produced bile at the ampulla. The mucosa was not remarkable. The extrahepatic ducts were normal.

Spleen The spleen was approximately twice the normal size and weighed 450 Gm. The capsule was wrinkled and blue. The spleen was soft in consistency. On cut section the malpighian corpuscles were not distinct, little of the pulp could be removed by scraping.

Bone Marrow A portion of the femur was removed and showed relatively firm red hyperplastic marrow replacing most of the fat normally present in the medullary cavity.

Other Organs The gastro-intestinal tract, pancreas, kidneys, aorta, thyroid, thymus, pituitary, adrenals, testes and brain showed no abnormalities.

Microscopic Postmortem Examination—*Liver* There were degenerative changes in the parenchymal cells of the liver. There were no unusual cellular collections in the portal spaces.

Spleen The structure was greatly distorted, mainly in the pulp spaces, which were replaced by a relatively solid but somewhat reticulated stroma in which were many large undifferentiated cells, myeloblasts, eosinophilic myelocytes and small multinucleated cells. The malpighian corpuscles were scarcely recognizable.

Lymph Node There was a partial loss of normal architecture, and the lymphoid follicles were almost completely obliterated. The sinuses were filled with undifferentiated cells similar to the cells described as present in the spleen.

Femoral Bone Marrow The fat had been entirely replaced by a fairly dense reticulated structure which held many cells that were slightly larger than plasma cells but with an acidophilic cytoplasm. These cells were apparently differentiating into the myeloid series, for myeloid cells could be detected. Few cells of the erythropoietic series were visible. There were numerous small vascular channels in the framework. Megalokaryocytes were rare, but there was a fair number of giant cells, each with several nuclei, which might have been megalokaryocytes or degenerating cells of the myeloid series.

Costal and Sternal Bone Marrow There was marked hyperplasia of leukopoietic cells and replacement of the little fat that is often present. There were a few megalokaryocytes like those present in the femoral marrow, but they were small and poorly formed. The predominant cell was large and polygonal, with a fairly dense cytoplasm and a deeply stained oval nucleus. Myelocytes could be distinguished, but there was little evidence of erythropoiesis. The marrow in general showed a proliferation of the reticular elements with the formation of a relatively dense framework. The appearances of the femoral, costal and sternal bone marrow were very similar, perhaps more marked alteration had occurred in the femoral marrow.

Postmortem Diagnosis The diagnosis was myelogenous leukemia—clinically aleukemia, with involvement of the bone marrow, spleen and lymph nodes.

Comment—During the three months this patient was under observation in the hospital he had persistent leukopenia and profound anemia without splenomegaly until shortly before death. Within the last twenty-four hours of life the tip of the spleen became barely palpable. During the early part of the patient's illness it was thought by some of the members of the staff that he might have an unusual form of pernicious anemia, but the number of erythrocytes failed to increase after the parenteral administration of liver extract. Other members of the staff favored the diagnosis of aplastic anemia. The occurrence of immature forms of leukocytes in the stained blood film and the finding of myeloid hyperplasia in the bone marrow of the sternum removed for biopsy were consistent with the diagnosis of aleukemic leukemia.

CASE 3—M. C., a white American man aged 47, entered the University of California Hospital on Feb. 18, 1936, complaining of weakness and dyspnea on exertion. He stated that he had felt well until early in December 1935, when he noticed progressive ease of fatigability, dyspnea and occasional cardiac palpitation. His physician told him his liver was enlarged and that he was anemic. For this condition the patient was given injections of liver extract, but there was no relief of symptoms. When the patient was admitted to the hospital it was learned that he had been employed as a member of a steel construction crew, but he denied knowledge of exposure to lead or fumes of benzene. There was no history of recent infection. He had subsisted on a well balanced diet.

Physical Examination—The patient appeared well developed and well nourished. There was marked pallor of the skin and mucous membranes, but no petechial hemorrhages were seen. Slight gingivitis was present, but there was no oozing of blood from the gums. There was no evidence of infection in the throat. No enlarged lymph nodes could be felt in the cervical or axillary regions, but a few slightly enlarged nodes were palpable in the inguinal regions. The edge of the liver was barely palpable, but the spleen could not be felt. The heart was not found to be enlarged on percussion, but a systolic murmur was audible over the mitral area.

Laboratory Data—The blood count showed hemoglobin, 24 per cent (3.4 Gm.) Sahli, erythrocytes, 870,000 per cubic millimeter, color index, 1.5, and leukocytes, 5,300 per cubic millimeter. The differential count showed segmented polymorphonuclear leukocytes, 32 per cent, nonsegmented leukocytes, 12 per cent,

lymphocytes, 46 per cent, monocytes, 8 per cent, and myeloblasts, 2 per cent. There were 102 nucleated red blood cells per hundred white blood cells, and the icteric index was 10. An analysis of the gastric secretion revealed the presence of free hydrochloric acid. Fragility of the erythrocytes began at a concentration of 0.45 per cent of sodium chloride and was complete at 0.35 per cent. Roentgenograms of the teeth and chest failed to show any remarkable change. Roentgenograms of the abdomen did not demonstrate enlargement of the spleen. There was no evidence of an organic lesion in the gastro-intestinal tract on fluoroscopic examination after an opaque meal. Roentgenograms taken of the left humerus and femur did not show atrophy of any quality or quantity in either the cortical

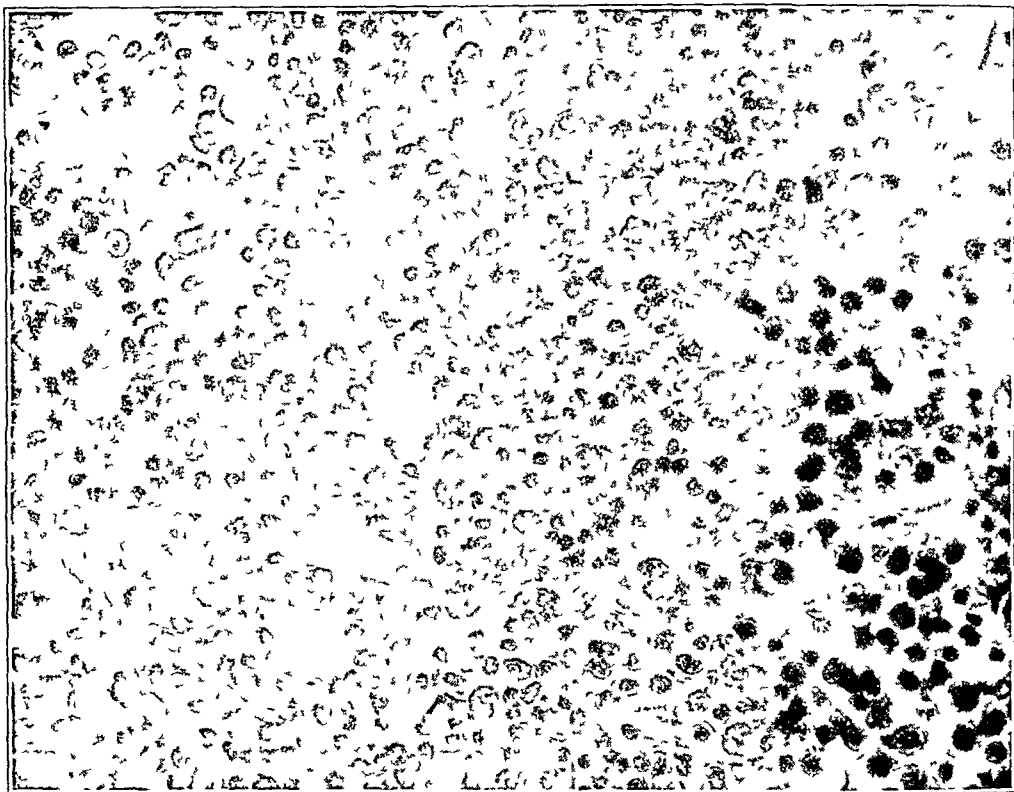


Fig 2 (case 3)—Photomicrograph of sternal marrow removed for biopsy, $\times 300$. There are large numbers of myeloblasts and large, round undifferentiated reticular cells.

or the medullary portions. The rose bengal dye was used in a test of hepatic function, which showed 58 per cent retention at the end of eight minutes and 28 per cent at the end of sixteen minutes (normal range).

Clinical Diagnosis—The final clinical diagnosis was aleukemic myelosis.

Biopsy of Sternal Marrow—Examination of the sternal marrow revealed areas of bone surrounded by hyperplastic bone marrow. Large mononuclear cells of the myeloid series were numerous, their cytoplasm contained granules which stained eosinophilic, slightly acidophilic, neutrophilic or basophilic. Many myeloblasts also were present. Almost equally numerous were nucleated red blood cells or normoblasts. Few adult polymorphonuclear leukocytes were present. The diagnosis was involvement of the bone marrow consistent with aleukemic myelosis.

Course of the Illness—The patient's general condition remained essentially the same as on entry. No change was observed after the administration of liver extract both by mouth and parenterally, cevitic acid both by mouth and parenterally and the oral administration of reduced iron, 3.2 Gm daily. On March 10, however, after a transfusion of 500 cc of whole blood, slight improvement was noted. The blood count on March 16 showed hemoglobin, 36 per cent, erythrocytes, 1,680,000, and leukocytes, 5,000. The differential count showed segmented polymorphonuclear leukocytes, 34 per cent, nonsegmented leukocytes, 12 per cent, polymorphonuclear basophils, 2 per cent, lymphocytes, 32 per cent, monocytes, 2 per cent, myeloblasts, 14 per cent, promyelocytes, 2 per cent, and unclassified cells, 2 per cent. There were 60 nucleated red blood cells per hundred white blood cells.

The patient was discharged from the hospital to return home. Throughout the period of observation the temperature remained subnormal in the mornings but rose as high as 38.2 C (100.8 F) in the afternoons. Death occurred suddenly on April 10. Postmortem examination was refused.

Clinical Diagnosis—The final clinical diagnosis was aleukemic myelosis.

CASE 4—H. W. C., a white American man aged 49 years, entered the University of California Hospital on Feb. 24, 1936, because of weakness, dyspnea on exertion and loss of weight. He was proud of the fact that he had not been ill since he was 18 years old, when he had typhoid. His illness started three months prior to entry, when he noted the gradual onset of weakness and mild dyspnea while climbing stairs. A physician told him that his hemoglobin value was 40 per cent and placed him on liver and iron therapy. He continued to fail in strength, and lost 25 pounds (11 Kg) in weight.

Physical Examination—The patient appeared well developed and well nourished, despite the history of loss of weight. There was pallor of the skin and mucous membranes. There was no demonstrable enlargement of the superficial lymph nodes. There was no evidence of infection about the gums or in the throat. Other than the presence of a soft blowing systolic murmur at the apex, examination of the heart showed nothing abnormal. Neither the spleen nor the liver was enlarged.

Laboratory Data—The blood count showed hemoglobin, 70 per cent (9.8 Gm) Sahli, erythrocytes, 2,910,000 per cubic millimeter, leukocytes, 3,750 per cubic millimeter. The differential count showed segmented polymorphonuclear leukocytes, 24 per cent, nonsegmented leukocytes, 14 per cent, eosinophils, 1 per cent, lymphocytes, 54 per cent, and monocytes, 7 per cent. The icteric index was 4.4. Hemolysis of red blood cells began at a concentration of 0.35 per cent sodium chloride and was complete at 0.25 per cent. Fluoroscopic examination and roentgenograms of the thoracic cavity and gastro-intestinal tract showed no signs of lesions, and no enlargement of the spleen could be demonstrated.

Course of the Illness—The patient's temperature was normal except for a daily rise in the afternoon to 37.4 C (99.3 F). The anemia and leukopenia were not affected by the parenteral administration of liver extract or the oral administration of reduced iron. During the patient's stay in the hospital the blood count remained essentially the same, but an occasional myeloblast was observed in the stained blood films.

Biopsy of Sternal Bone Marrow—The bone marrow showed a normal structure but was much more cellular than usual. Myeloid cells from the promyelocyte to the young leukocyte predominated and were numerous. Many mitotic figures were seen. Erythroblastic cells appeared in moderate number. The diagnosis was aleukemic myelosis.

Subsequent Course of the Illness—The patient was discharged from the hospital on March 14, and he returned to the outpatient department on August 21, at which time his physical appearance was essentially the same. There was no apparent enlargement of the lymph nodes, liver or spleen. The blood count showed hemoglobin, 65 per cent (92 Gm.) Sahli, erythrocytes, 1,700,000 per cubic millimeter, leukocytes, 3,600 per cubic millimeter, and platelets, 100,000. The differential count showed segmented polymorphonuclear leukocytes, 1 per cent, nonsegmented leukocytes, 14 per cent, lymphocytes, 35 per cent, monocytes, 3 per cent, myelocytes, 7 per cent, myeloblasts, 30 per cent, and unclassified forms, 10 per cent. There were 7 nucleated red blood cells per hundred white blood cells.

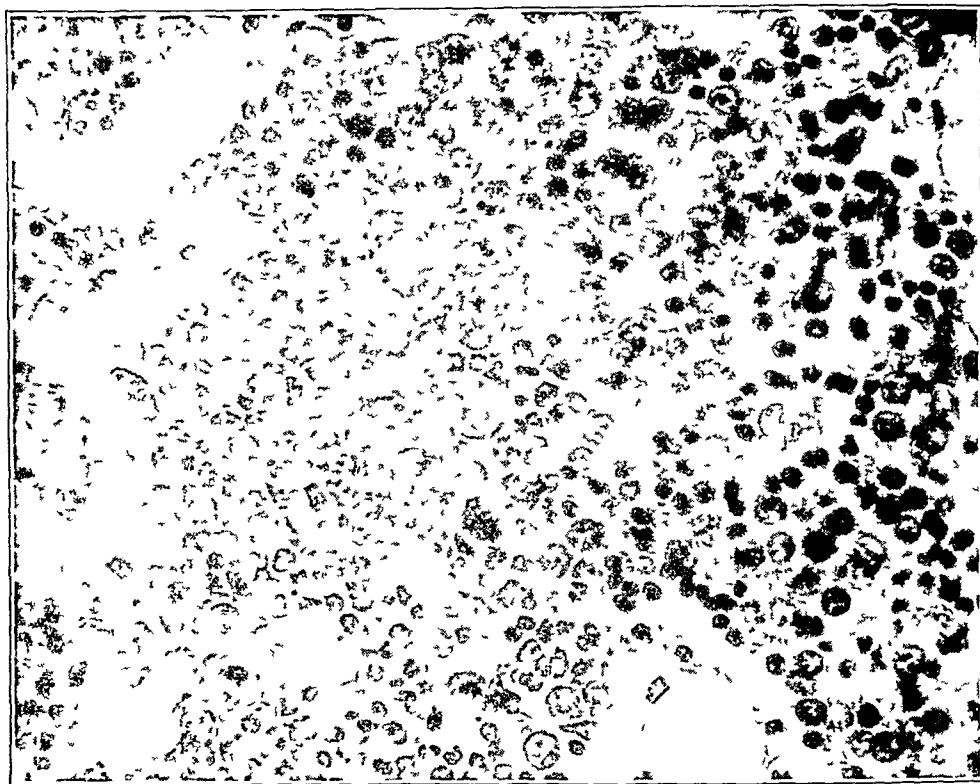


Fig 3 (case 4)—Marked myeloid hyperplasia of the specimen of marrow removed from the sternum for biopsy, $\times 300$. There are large numbers of myeloblasts and undifferentiated reticular cells.

Clinical Diagnosis—The clinical diagnosis was aleukemic myelosis.

CASE 5—J. R., a white man aged 66, was admitted to the University of California Hospital on Nov 30, 1936, complaining of weakness and dizziness of six weeks' duration. He was seen in the outpatient department on November 24, where the following diagnosis was made: (1) pernicious anemia and (2) bilateral hydrocele. This patient had been well until six weeks prior to entry into the hospital, when he noticed the gradual onset of weakness and dizziness. About November 1 he found it difficult to walk a short distance without support. During the week prior to entry he fainted three times. At the age of 16 he contracted gonorrhea, for which he received treatment, and he stated that at the age of 18 he had a chancre which subsided without treatment.

Physical Examination—The patient appeared well developed and moderately well nourished. There was no evidence of infection in the skin, ears, nose or throat. There was marked caries of the teeth, and the gums showed moderate swelling and increased vascularity. The heart was not found to be enlarged on percussion. The blood pressure was 132 systolic and 74 diastolic. The edge of the liver was felt 2 cm below the right costal margin and was smooth and slightly tender. The spleen was not felt on deep palpation. Lymph nodes averaging from 1 to 2 cm in diameter were present in both inguinal regions. Elsewhere in the cervical and axillary regions the lymph nodes averaged less than 0.5 cm in diameter.

Laboratory Data—The blood count showed hemoglobin, 28 per cent (3.92 Gm.) Sahli, erythrocytes, 1,180,000 per cubic millimeter, and leukocytes, 1,250 per cubic millimeter. The differential count was segmented polymorphonuclear leukocytes, 16 per cent, nonsegmented leukocytes, 20 per cent, lymphocytes, 44 per cent, monocytes, 4 per cent, myelocytes, 4 per cent, and myeloblasts, 12 per cent. The color index was 1.18, the volume index 1.12, the mean corpuscular volume 101 and the mean corpuscular concentration 32 per cent. The platelets were moderately diminished in number, and the reticulocyte value was 0.8 per cent. The Wassermann and Kahn tests of the blood for syphilis gave positive reactions. There was an absence of free hydrochloric acid and pepsin from the gastric secretion after the administration of histamine.

Course of the Illness—On December 5 the patient was given a transfusion of 500 cc of whole blood, which was followed by relief of symptoms. There was no increase in the percentage of reticulocytes after the parenteral administration of liver extract.

While the patient was under observation in the hospital there was a gradual rise in the leukocyte count to a level of 4,000 cells per cubic millimeter. Associated with this was a shift in the differential formula to include higher percentages of immature forms. The patient was discharged from the hospital on December 30, at which time there were 30 per cent of myeloblasts in the stained blood film. It was of interest that many of these cells contained Auer bodies.

Clinical Diagnosis—The diagnosis was aleukemic myelosis.

Biopsy of Sternal Marrow—Sections showed markedly increased cellularity of the marrow and almost complete absence of fat cells. There were a large number of megakaryocytes scattered throughout the marrow. Many mature polymorphonuclear leukocytes were present. A large number of cells that were considered to be myeloblasts also was noted, among groups of these cells mitotic figures were noted. In addition to these cells there were many reticular cells. A few small areas of erythropoiesis were seen. It was concluded that the sternal marrow showed myeloid hyperplasia consistent with aleukemic myelosis.

Comment—The presence of macrocytic anemia combined with achylia gastrica in this patient suggested the diagnosis of pernicious anemia. However, the erythrocytes and hemoglobin values failed to increase after the parenteral administration of liver extract. In the differential diagnosis it was thought possible, because of the slight generalized lymphadenopathy, that the abnormality of hematopoiesis resulted from reticulo-endotheliosis. Throughout the patient's stay in

the hospital there was a gradual shift to the left in the differential formula to include 30 per cent of myeloblasts. This evidence from the stained film supported the diagnosis of aleukemic myelosis.

SYMPTOMATOLOGY

The symptoms as they occurred in the patients are recorded in the histories. It is to be noted that the disease was insidious in onset. The most frequent complaint was that of gradually developing weakness extending over a period of from three to nine months. During the

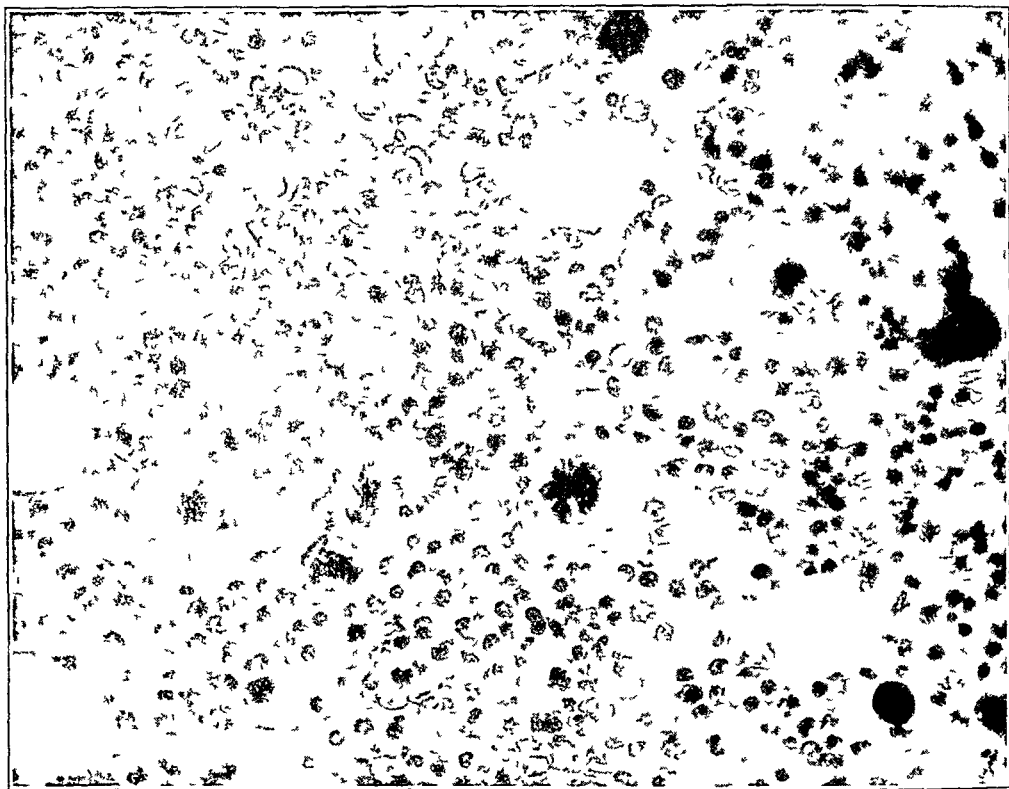


Fig 4 (case 5)—Sternal marrow removed for biopsy, $\times 300$. There is an increase in the number of immature myeloid forms and megakaryocytes.

course of the illness the patients became distressed by palpitation and dyspnea. There was little tendency toward remission or exacerbation of symptoms except when a sense of well-being followed transfusions of whole blood. Bleeding into the skin and from the mucous membranes occurred in two of the patients. It is worthy of note that all the patients were in a fair state of nutrition and did not have the cachectic appearance usually found in patients with neoplastic malignant growths or prolonged infection. In one patient there was moderate enlargement of the cervical lymph nodes, but in none was there clinical

evidence of enlargement of the spleen. The gums of one patient were swollen and bleeding, but there were no signs of gingivitis.

BLOOD PICTURE

From the accompanying table it will be seen that severe anemia was present in all the patients, the degree depending on the duration of illness and on whether or not a transfusion had been recently administered. The erythrocytes varied in number from a high level of 2,900,000 cells to as low as 500,000 cells per cubic millimeter, depending on the individual patient. The level of hemoglobin was reduced proportionately.

Hematologic Data

Case	Date	Hemo- globin		Red Blood Cells, Mil- lions per Cu. Mm	Platelets per Cu. Mm	White Blood Cells, per Cu. Mm	Polymor- phonuclear Leuko- cytes, %		Eosinophils, %	Lymphocytes, %	Monocytes, %	Myelocytes, %	Myeloblasts, %	Unclassified Cells, %	Nucleated Erythrocytes per 100 Leukocytes
		%	Gm				Segmented	Nonsegmented							
1	2/ 2/32*	94	12.9	4.31	40,000	7,600	39	2		45	3	4	5	2	1
	2/25/32	50	7.0	1.78		1,700	44	20	2	16	2	10	6		1
	3/ 3/32	65	8.9	2.30	30,000	1,350	18	23	4	25	4	18	6	2	2
2	7/20/33	55	7.7	2.86		2,300	7	22		42	26	1		2	2
	9/ 5/33	43	5.9	2.46		2,450	2	14	1	23	14	10	3	28	2
	10/24/33	10	1.4	0.50	40,000	980	8	28		16	12	20	16		
3	2/18/36	24	3.4	0.87	-	5,300	32	12		46	8		2		102
	3/16/36	36	5.1	1.68		5,000	34	12	2	32	2	2	14	2	60
4	2/24/36	70	9.8	2.91		3,750	24	14	1	54	7				
	8/21/36	65	9.2	1.70	100,000	3,600	1	14		35	3	7	30	10	7
5	12/ 1/36	28	3.9	1.18	120,000	1,250	16	20		44	4	4	12		
	12/17/36	32	4.5	1.76	304,000	3,150	5	18	2	33	2	4	30	6	2

* The patient received three transfusions of 500 cc each of whole blood during the week prior to this examination.

less than that of the erythrocytes, so that the color index ranged from approximately 1 to 1.5. There was moderate to marked variation in the size and in the shape of the red blood cells. There were a great many large, round and definitely oval erythrocytes that were well filled with hemoglobin, and by contrast other cells appeared much smaller than normal. Nucleated red blood cells were noted in the stained films in all the cases, and in one instance there were as many as 102 per hundred white blood cells. The leukocyte count did not in any case exceed 5,300 cells per cubic millimeter, and the lowest count recorded was 980 per cubic millimeter.

In our cases, irrespective of the fact that leukocytosis was not present, it is to be noted that the qualitative changes in the differential formulas were similar to those typical of true leukemia. There was a shift to the left in the granulocytes to include myelocytes and myelo-

blasts The immature forms comprised from 2 to 47 per cent of the total cells, which in the presence of leukopenia indicates an absolute increase of considerable degree

There was a great reduction in the number of platelets in the blood of all our patients This was accompanied in two cases with the usual manifestations of thrombocytopenic purpura, namely, spontaneous bleeding, prolongation of the time required for a clot to form and failure of the clot to retract properly

BIOPSY OF BONE MARROW

Specimens of bone marrow from the sternum were obtained in four cases by the removal of a "button" of bone with a trephine having a 15 mm bore After removal, spread preparations were made on slides and cover slips for immediate staining and examination Other pieces of marrow tissue were fixed in Zenker's fluid and at the appropriate time embedded in paraffin, sectioned and stained with hematoxylin and eosin The two methods afforded an opportunity to study the finer cytologic structure together with the architectural arrangement of the marrow cells

Photomicrographs are shown in figures 1 to 4 and correspond to case histories 2 to 5, respectively In each of the sections the normal fatty tissue has been replaced by hyperplastic marrow In general, the predominant type of cell contains a large vesicular nucleus in which may be seen masses of chromatin and in many cells 1 or more darkly stained nucleoli The cytoplasm may vary in amount but usually consists of a narrow rim taking a light blue stain These cells often appear in groups, and among them may be seen an occasional mitotic figure When compared with "touch preparations" of fresh material on cover slips stained with Wright's stain, the cells may be identified as myeloblasts and early myelocytes Comparatively few segmented forms are to be seen Small groups of erythroblasts and normoblasts may be distinguished, but they play a less prominent rôle

COMMENT

The leukemia in each of the five cases recorded here, it is believed, belonged to the myeloid group but differed from the usual form of the disease in that neither leukocytosis nor splenomegaly was present These cases are reported because of their rarity and because of the difficulties encountered clinically in making a differential diagnosis from aplastic anemia or from certain conditions associated with a leukemoid blood picture, such as reticulo-endotheliosis, metastatic tumor nodules in the bone marrow,⁸ osteosclerosis,⁸ myelofibrosis⁹ and abnormal

8 Mavros, A Aleukamische, besser "nichtleukamische" Myelose mit Osteosklerose, *Folia haemat* 43 323, 1931

leukopoiesis associated with infection¹⁰ For none of the patients, however, was there a history of chronic loss of blood, the presence of obvious infection or a demonstrable neoplastic process to account for the abnormal leukopoiesis

It is to be emphasized that the diagnosis of this unusual manifestation of leukemia depends largely on the differential formula For a patient with a greatly reduced total leukocyte count, a time-consuming and painstaking examination of the stained film is required in order to obtain a complete analysis of leukopoietic activity In the cases reported here the diagnosis of aleukemic myelosis was considered tenable after the detection of myeloblasts, of a definite shift to the left in the leukocytes associated with severe anemia and of signs of regeneration of the erythrocytes

Biopsy of marrow removed from the sternum affords an invaluable aid in establishing the diagnosis Specimens of marrow showing a predominance of undifferentiated types of cells, many of which contain mitotic figures, packed solidly together to the exclusion of fat cells, enable the pathologist to render an opinion as to the nature of the hyperplasia of the marrow

Since leukemia is considered a systemic disease, the usual structural changes are those of myeloid hyperplasia of the marrow associated with variable degrees of infiltration in the viscera, meninges and skin The clinical manifestations, therefore, may be protean, depending on the degree of change occurring in different organs It may be assumed, then, that myeloid metaplasia in the spleen may be of minimal amount, thus accounting for another unusual manifestation of leukemia

SUMMARY

A description is given of five cases of leukemia in patients without leukocytosis and without splenomegaly The clinical findings were those of severe anemia, thrombopenia and leukopenia with the presence of immature forms of leukocytes in the stained films of blood Myeloid hyperplasia of the bone marrow consistent with leukemia was demonstrated by histologic examination of specimens removed from the sternum for biopsy

Dr C L Connor, of the Division of Pathology, gave us permission to use the postmortem and histologic data

9 Mettier, S R, and Rusk, G Y Fibrosis of the Bone Marrow (Myelofibrosis) Associated with a Leukemoid Blood Picture, *Am J Path* **13** 377 (May) 1937

10 Krumbhaar, E B Leukemoid Blood Pictures in Various Clinical Conditions, *Am J M Sc* **172** 519, 1926 Thompson, W P Abnormalities in the White Blood Cell Response Leukemoid, Atypical Leukemic and Leukopenic Blood Pictures, *ibid* **182** 334, 1931

INFLUENCE OF COPPER AND A LIVER FRACTION ON RETENTION OF IRON

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The influence of copper on the formation of hemoglobin is a problem which has not been completely solved, and the literature abounds in conflicting reports on the subject. Elvehjem¹ has recently summarized the work on the biologic significance of copper, and the reader is referred to this paper for a comprehensive review and bibliography. It has been found that in the experimental nutritional anemia of animals neither iron nor copper alone is effective in producing regeneration of hemoglobin, but when iron is given in combination with a small amount of copper a rapid increase in the hemoglobin content of the blood ensues. The work of Whipple² on experimental hemorrhagic anemia in dogs has not entirely confirmed these results. He found that in certain instances a combination of iron and copper was more beneficial than iron alone but that this was not consistently true. It is possible that a sufficient amount of copper may be obtained by these animals from unrecognized sources and as a contaminant of iron preparations to supply the small amount necessary for the formation of hemoglobin and so account for the beneficial effects apparently obtained from iron alone.

The effect of copper on the storage and retention of iron is no better understood than is its rôle in the formation of hemoglobin. It has been demonstrated in animals that copper does not increase the retention of iron when the two metals are given together,³ but it does cause an

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This work was begun in association with Dr C W Baldrige, who died on Nov 22, 1934

1 Elvehjem, C A. The Biological Significance of Copper and Its Relation to Iron Metabolism, *Physiol Rev* **15** 471, 1935

2 Robschert-Robbins, F S, Elden, C A, Sperry, W M, and Whipple, G H. Blood Regeneration in Severe Anemia. XII. Potent Influence of Inorganic Ash of Apricots, Liver, Kidney and Pineapple, *J Biol Chem* **79** 563, 1928. Elden, C A, Sperry, W M, Robschert-Robbins, S F, and Whipple, G H. Blood Regeneration in Severe Anemia. XIII. Influence of Certain Copper Salts upon Hemoglobin Output, *ibid* **79** 577, 1928.

3 Josephs, H W. Studies on Iron Metabolism and the Influence of Copper, *J Biol Chem* **96** 559, 1932.

increased proportion of the iron to be used in the production of hemoglobin. When copper alone is given to an animal that has previously received iron, there is a reduction in the iron content of the liver.⁴ These findings suggest that while copper does not greatly influence the retention of iron, it does affect its mobilization and utilization.⁵

Excellent clinical results have been reported in the treatment of hypochromic anemia by the administration of a combination of iron and copper,⁶ although other investigators have felt that this combination has no advantage over iron alone. It has been assumed that sufficient copper is present in the food and as a contaminant of iron-containing drugs to supply all that is needed for hemoglobin regeneration, but Bethell⁷ reported that the efficacy of iron in hypochromic anemia was not lessened when it was given in the form of reduced iron and in conjunction with a diet low in copper. Although Elvehjem concluded that "copper is necessary as a supplement to iron in hemoglobin formation in red-blooded animals," the evidence seems to favor the view that sufficient amounts are obtained from ordinary sources, so that additional copper medication is unnecessary.

Equally confusing are the reports on the effect of liver and liver extract in hypochromic anemias. Whipple⁸ has shown that liver and certain liver fractions are potent in producing a regeneration of hemoglobin in the dog but that supplementing this liver fraction with iron may still further increase the output of hemoglobin. It has been shown also that a combination of liver and iron is effective in the nutritional anemia of rats.⁹ Keefer¹⁰ has demonstrated that this combination is more effective than iron alone in some cases of hypochromic anemia, while in others the addition of liver is unnecessary. Cheney and

4 Elvehjem, C. A., and Sherman, W. C. The Action of Copper in Iron Metabolism, *J Biol Chem* **98** 309, 1932.

5 Cook, S. F., and Spiles, N. M. Some Factors Regulating the Utilization of Splenic Iron, *Am J Physiol* **98** 626, 1931.

6 Mills, E. S. The Treatment of Idiopathic (Hypochromic) Anemia with Iron and Copper, *Canad M A J* **22** 175, 1930. Elvehjem¹.

7 Bethell, F. H., Goldhamer, S. M., Isaacs, R., and Sturgis, C. C. The Diagnosis and Treatment of the Iron-Deficiency Anemias, *J A M A* **103** 797 (Sept 15) 1934.

8 Whipple, G. H., Robschey-Robbins, F. S., and Walden, G. B. Blood Regeneration in Severe Anemia. XXI. A Liver Fraction Potent in Anemia Due to Hemorrhage, *Am J M Sc* **179** 628, 1930.

9 Hart, E. B., Steenbock, H., Waddell, J., and Elvehjem, C. A. Iron in Nutrition. VII. Copper as a Supplement to Iron for Hemoglobin Building in the Rat, *J Biol Chem* **77** 797, 1928.

10 Keefer, C. S., and Yang, C. S. The Treatment for Secondary Anemia. *Arch Int Med* **48** 537 (Oct) 1931, The Value of Liver and Iron in the Treatment of Secondary Anemia, *J A M A* **93** 575 (Aug 24) 1929.

Niemand¹¹ recommended the combination in cases of posthemorrhagic anemia, but Powers and Murphy¹² said they believed the addition of liver is of no value, and Bethell⁷ found that simple preparations of iron gave results that compared favorably with the results obtained with iron in combination with other substances. Studies of the iron balance¹³ in infants show that breast milk facilitates the absorption of iron from the gastro-intestinal tract, that copper does not influence the iron balance but that liver extract causes an improvement in the retention of iron. The present investigation was undertaken to obtain further information on these problems as they are applied to hypochromic anemia of adults.

The essential clinical and hematologic data for each patient are given in tables 1 and 2. The methods of study were the same as those employed in

TABLE 1—*Clinical Features*

Patient	Age	Sex	Diagnosis	Clinical Features
1	26	F	Idiopathic hypochromic anemia	No history of unusual loss of blood, adequate diet, palpable spleen, koilonychia, free hydrochloric acid in gastric contents only after administration of histamine, idiopathic epilepsy
2	48	F	Hypochromic anemia, hemorrhage	Chronic bronchitis of four years' duration, mild atrophic arthritis, no abnormal loss of blood
3	48	F	Hypochromic anemia, hemorrhage	Gastric distress for two years with roentgenographic evidence of gastric ulcer, profuse menstruation
4	34	F	Hypochromic anemia, hemorrhage	Menorrhagia
5	34	F	Idiopathic hypochromic anemia	No history of unusual loss of blood, had bruised easily for years, koilonychia present for seven years, dysphagia
6	40	F	Hypochromic anemia	Minimal pulmonary tuberculosis in apex of left lung
7	41	F	Idiopathic hypochromic anemia	No history of unusual loss of blood, palpable spleen, no pregnancies, achlorhydria, one sister had anemia
8	23	F	Hypochromic anemia, hemorrhage	Had one child and three miscarriages, was pale and lost considerable blood with each pregnancy, menses irregular
9	40	F	Idiopathic hypochromic anemia	No unusual loss of blood, dysphagia, hypochlorhydria, ten pregnancies, was pale and weak with each, did not regain strength after last pregnancy three years previously
10	45	F	Hypochromic anemia, hemorrhage	Menorrhagia

previously reported determinations of iron balance,¹⁴ and the same diets were used throughout. The patients were placed on this diet for a three day period of adjustment before the balance studies were begun, and this was followed by

11 Cheney, G, and Niemand, F. The Treatment of Secondary Anemia with 'Secondary Anemia Liver Extract' and Iron, *Am J M Sc* **184** 314, 1932

12 Powers, J H, and Murphy, W P. The Treatment of Secondary Anemia, *J A M A* **96** 504 (Feb 14) 1931

13 Maurer, S, Greengard, J, Curtiss, W F, and Kluver, C. The Effect of Small Quantities of Breast Milk, Liver Extract, Iron and Copper, Respectively and in Combinations, upon the Iron Balance of Artificially Fed Infants, *J Pediat* **4** 356, 1934

14 (a) Fowler, W M, Barer, A P, and Spielhagen, G F. Retention and Utilization of Small Amounts of Orally Administered Iron, *Arch Int Med* **59** 1024 (June) 1937. (b) Fowler, W M, and Barer, A P. Retention and Utilization of Orally Administered Iron, *ibid* **59** 561 (April) 1937

TABLE 2—*Hematologic and Laboratory Data*

Patient	Hemo- globin, Percentage	Hematocrit Reading, Percentage	Erythro- cytes, Percentage	Color Index	Volume Index	Satura- tion Index	Gastric Acidity	Basal Metabolic Rate
1	46	68	106	0 43	0 64	0 67	Low	+13
2	58	79	89	0 65	0 88	0 73	Low	+ 8
3	31	49	68	0 45	0 72	0 63	Low	- 2
4	43	65	74	0 58	0 87	0 66	Normal	-17
5	39	57	89	0 43	0 64	0 68		- 8
6	34	51	82	0 41	0 62	0 66	0	-16
7	39	65	88	0 44	0 73	0 60	0	
8	53	68	78	0 67	0 87	0 77	Low	
9	43	69	79	0 54	0 87	0 62	Low	
10	16	31	48	0 33	0 64	0 51	0	

TABLE 3—*Detailed Results of Balance Studies*

Patient	Period	Nitrogen, Mg per Day			Phosphorus, Mg per Day			Iron, Mg per Day			Erythro- cytes, Mil lions Cu Mm	Hemo- globin, Gm per 100 Cc
		In- take	Excre- tion	Bal- ance	In- take	Excre- tion	Bal- ance	In- take	Excre- tion	Bal- ance		
1	1	10 57	11 63	-1 06	1 59	1 76	-0 17	12 3	10 6	+ 1 7	5 29	6 525
	2	11 48	11 39	+0 09	1 74	2 27	-0 53	246 5	206 0	+ 40 5	4 39	6 545
	3	10 48	10 79	+0 69	1 74	2 29	-0 55	246 4	244 9	+ 1 5	4 79	6 735
	4	9 95	9 16	+0 79	1 44	2 09	-0 65	217 0	285 9	- 68 9	5 35	7 275
	5*	10 10	10 77	-0 67	1 43	1 38	+0 05	517 7	241 0	+276 7	5 55	8 570
2	1	9 80	7 74	+2 06	1 44	1 02	+0 42	12 0	7 3	+ 4 7	4 44	8 150
	2	9 93	7 11	+2 82	1 44	1 19	+0 25	217 1	87 4	+129 7	4 28	7 275
	3	9 91	6 95	+2 96	1 44	1 00	+0 44	221 7	173 9	+ 47 8	4 82	8 230
	4	10 59	8 31	+2 28	1 49	1 12	+0 37	260 8	337 2	- 76 4	5 03	8 340
	5	10 79	8 88	+1 91	1 50	1 05	+0 45	260 9	187 2	+ 73 7	4 92	9 770
3	1	9 80	9 62	+0 18	1 44	1 22	+0 22	12 0	14 3	- 2 3	3 40	4 360
	2	9 93	7 40	+2 53	1 44	1 14	+0 30	217 1	231 1	- 14 0	3 92	4 360
	3	9 92	6 66	+3 26	1 44	0 73	+0 71	216 9	130 9	+ 86 0	4 10	6 385
	4	10 59	10 27	+0 32	1 49	0 97	+0 52	260 8	341 1	- 80 3	4 35	7 190
	5	10 79	9 25	+1 54	1 50	1 07	+0 43	260 9	218 4	+ 42 5	5 01	7 800
4	1	9 80	10 91	-1 11	1 44	1 25	+0 19	12 0	9 8	+ 2 2	3 69	6 200
	2	9 93	9 27	+0 66	1 44	1 12	+0 32	217 1	160 7	+ 56 4	4 01	6 805
	3	9 90	8 22	+1 68	1 44	0 79	+0 65	230 5	173 9	+ 56 6	3 88	7 100
	4	10 59	9 01	+1 58	1 49	1 34	+0 15	260 8	364 0	-103 2	3 98	8 115
	5	10 79	9 10	+1 69	1 50	1 01	+0 49	260 9	237 2	+ 23 7	4 25	8 680
5	1	9 78	9 46	+0 32	1 44	1 14	+0 30	11 9	13 3	- 1 4	4 47	5 595
	2	11 08	8 80	+2 28	1 44	0 96	+0 48	426 7	117 0	+309 7	4 48	5 855
	3	10 78	9 29	+1 49	1 44	1 55	-0 11	426 6	137 2	+289 4	4 85	6 455
6	1	9 78	11 87	-2 09	1 44	1 26	-0 18	11 9	21 7	- 9 8	4 10	4 785
	2	10 08	10 21	-0 12	1 44	1 48	-0 04	517 7	235 1	+282 6	4 37	5 595
	3	10 08	10 13	-0 05	1 44	1 34	+0 10	517 7	394 1	+123 6	4 55	5 645
	4	10 08	10 03	+0 05	1 44	1 35	+0 09	517 7	234 2	+283 5	4 67	7 450
	5	10 08	9 60	+0 48	1 44	1 65	-0 21	517 7	198 9	+318 8	4 71	8 680
	6	10 08	9 52	+0 56	1 44	1 58	-0 14	517 7	187 3	+330 4	4 99	10 370
	7	10 08	10 06	+0 02	1 44	1 66	-0 22	517 7	397 4	+120 3	5 17	9 470
	8†	10 08	11 29	-1 21	1 44	1 14	+0 30	517 7	420 6	+ 97 1	4 71	11 570
	9	10 08	12 56	-2 48	1 44	1 52	-0 08	517 7	617 2	- 99 5	4 74	12 200
7	1	9 79	9 77	+0 02	1 45	0 97	+0 48	12 0	40 8	- 28 8	4 41	5 595
	2	11 03	9 11	+1 92	1 47	1 22	+0 25	281 8	221 1	+ 60 7	4 34	5 595
	3	11 04	7 44	+3 60	1 48	1 09	+0 39	281 9	260 6	+ 21 3	4 45	5 823
	4	10 88	7 28	+3 60	1 48	0 98	+0 50	275 9	197 5	+ 78 4	4 50	6 310
8	1	11 03	8 73	+2 30	1 63	1 23	+0 40	12 6	11 2	+ 1 4	3 92	7 540
	2	13 49	10 06	+3 43	1 84	1 20	+0 64	283 3	200 7	+ 82 6	3 87	7 800
	3	13 49	10 61	+2 88	1 84	1 25	+0 59	283 2	227 2	+ 56 0	4 23	9 020
	4	13 51	10 39	+3 12	1 84	1 13	+0 71	283 3	143 2	+140 1	3 93	8 905
	5	13 48	12 08	+1 40	1 83	1 55	+0 28	283 4	352 8	- 69 4	4 38	8 680
9	1	9 78	9 38	+0 40	1 44	1 23	+0 21	11 9	24 4	- 12 5	3 98	6 140
	2	10 88	10 37	+0 51	1 48	1 23	+0 25	273 9	148 6	+125 3	3 98	6 650
	3	10 88	8 71	+2 17	1 48	0 92	+0 56	273 9	167 4	+106 5	4 30	8 115
	4	11 69	7 28	+4 41	1 63	0 87	+0 76	274 4	163 9	+110 5	4 92	8 570
	5	11 35	9 05	+2 30	1 66	1 14	+0 52	274 7	163 8	+110 9	4 14	9 470
	6	11 32	10 52	+0 80	1 68	1 03	+0 65	274 7	300 3	- 25 6	4 17	10 070
10	1	9 78	8 67	+1 11	1 44	1 20	+0 24	11 9	8 9	+ 3 0	2 40	2 230
	2	10 79	9 50	+1 29	1 48	1 04	+0 44	275 9	192 2	+ 83 7	2 33	2 610
	3	11 04	9 11	+1 93	1 48	1 33	+0 15	263 9	236 3	+ 27 6	2 96	3 395
	4	11 04	9 71	+1 33	1 48	1 73	-0 25	263 9	227 3	+ 36 6	3 40	5 260
	5	11 04	9 35	+1 69	1 48	1 46	+0 02	263 9	220 4	+ 43 5	3 95	6 385
	6	11 04	10 03	+1 01	1 48	1 44	+0 04	263 9	170 3	+ 93 6	3 77	6 595
	7†	10 79	12 03	-1 24	1 48	1 22	+0 26	269 9	373 8	-103 9	5 22	10 940
	8	10 79	11 16	-0 37	1 48	1 24	+0 24	269 9	203 8	+ 66 1	5 23	11 360

* Iron and ammonium citrates given without copper

† Sixty six day interval between periods 7 and 8, medication continued

‡ Sixty five day interval between periods 6 and 7, medication continued

a six day control period, during which the iron ingested was obtained from the food alone. The subsequent balance periods were of six days' duration, and the results given in the tables show the average daily retention for that six day period. Patients 1 to 4 received 60 cc of an elixir of a copper and iron compound three times daily, which on analysis yielded from 217 to 260 mg of iron per day. Patient 1 during a fourth balance period received 3 Gm of iron and ammonium citrates per day with no copper. Patients 5 and 6 received an aqueous solution of iron and ammonium citrates and cupric sulfate of such strength that each 60 cc contained 15 mg of cupric sulfate and 1 Gm of iron and ammonium citrates, which supplied approximately 500 mg of iron per day. Patients 7 to 10 received iron plus a liver fraction¹⁵. This, on analysis, yielded from 263.9 to 283.4 mg of iron per day. The complete results of the balance studies are given in table 3, and a summary of the retention of iron by periods is given in table 4. The iron content of the copper and iron compound was in the form of ferric citrate while the iron in the liver preparation was iron and ammonium citrates.

TABLE 4—Average Daily Iron Balances in Milligrams

Patient	Control Period	Period 1	Period 2	Period 3	Period 4	Period 5	Period 6	Period 7	Period 8	Total Iron Balance
1	+ 17	+ 40.5	+ 15	- 68.9						- 162.0
2	+ 47	+129.7	+ 47.8	- 76.4	+ 73.7					1,048.7
3	- 23	- 14.0	+ 86.0	- 80.3	+ 42.5					205.0
4	+ 22	+ 56.4	+ 56.6	-103.2	+ 23.7					201.1
5	- 14	+309.7	+289.4							3,594.3
6	- 98	+282.6	+123.6	+283.5	+318.8	+330.4	+120.3*	+97.1	-99.5	8,740.8
7	-28.5†	+ 60.7	+ 21.3	+ 78.4						962.6
8	+ 14	+ 82.6	+ 56.0	+140.1	- 69.4					1,256.1
9	-12.5‡	+125.3	+106.5	+110.5	+110.9	- 25.6				2,566.6
10	+ 3.0	+ 83.7	+ 27.6	+ 36.6	+ 43.5	+ 93.6‡	-103.9	+66.1		1,483.0

* Sixty six day interval between periods 6 and 7 with continuous medication

† Menstrual loss of blood

‡ Sixty five day interval between periods 5 and 6 with continuous medication

COPPER

The first four patients received the iron and copper preparation in such amounts that the intake of iron ranged from 216.9 to 260.9 mg per day and the iron balances ranged from -14 to +129.7 mg per day during the first two balance periods. The average daily iron balance of the four patients for these two periods was +53.1 and +47.9 mg, respectively, which is slightly larger than was found in a previously reported group of patients receiving from 170.5 to 233.2 mg of iron per day without copper^{14a}. During the third balance period all the patients showed a markedly negative iron balance, and in no other group of patients has such a consistent drop been noted. Three of the patients studied during a fourth period returned to a positive balance. The average daily iron balance and the percentage of the iron retained by each of the four patients during the entire period of observation are given in table 5, and it will be noted that the retention is distinctly less for those patients receiving copper than for those of the other groups.

15 The preparation used was Iextron

Patient 1, in a fourth balance period, not recorded in table 4, received 5177 mg of iron per day with no copper and retained 2767 mg daily. This is comparable to the amount retained by patients previously reported on who received a similar amount of iron alone ^{14b}

Patients 5 and 6 received an aqueous solution of iron and ammonium citrates yielding 426 mg (patient 5) and 517 mg (patient 6) of iron per day plus 15 mg of cupric sulfate. The retention of iron was comparable to that which followed the administration of a similar amount of iron without additional copper ^{14b}

Patient 1 was in negative iron balance throughout the first three periods of observation but showed a moderate increase in the hemoglobin content of the blood. The percentage of the administered iron which was retained by patients 2 to 4 varied from 3.4 to 18.1 per cent (table 6). This is decidedly less than was retained by the previous

TABLE 5—Retention of Iron

Patient	Iron and Ammonium Citrates,* 170.6 to 183.9 mg of Iron Daily		Copper Plus Iron,† 216.9 to 260.9 mg of Iron Daily		Liver Extract Plus Iron, 263.9 to 283.4 mg of Iron Daily	
	Average Daily Iron Retention, Mg	Percentage of Iron Retained	Average Daily Iron Retention, Mg	Percentage of Iron Retained	Average Daily Iron Retention, Mg	Percentage of Iron Retained
1	55.7	30.5	0	0	53.4	19.0
2	43.2	23.6	43.6	18.1	52.3	18.4
3	42.6	23.2	8.5	3.5	85.5	31.1
4	82.8	45.1	8.3	3.4	35.3	13.2
5	44.7	27.1				
Av	53.7	29.9	15.1	6.2	55.3	20.4

* The data are taken from a preceding paper. Exclusive of patient 6, who received larger amounts of iron.

† Exclusive of patients 5 and 6, who received larger amounts of iron.

group of patients receiving no copper and a somewhat smaller amount of iron ^{14a}. The percentage retained by patients 5 and 6 was much greater and was comparable to that retained by those patients receiving a similar amount of iron without copper ^{14b}.

In studying the utilization of iron (table 6) we have again assumed that the blood volume of each patient was 5 liters and have calculated on this basis the approximate total increase in the hemoglobin content. The percentage of the iron used in the formation of hemoglobin varied from 2.5 to 9 per cent, with an average of 5.2 per cent for the first six patients (exclusive of patient 1). This should be compared with the 3.4 per cent utilization reported by Heath,¹⁶ the 1.9 per cent utilization from large doses of iron ^{14b} and the 9.1 per cent utilization from moderate doses of iron without copper ^{14a}. This average utilization of the administered iron does not present the entire picture in patients 1, 3 and 4. It was noted that there was a definite increase in the hemo-

16 Heath, C. W. Oral Administration of Iron in Hypochromic Anemia, Arch Int Med 51:459 (March) 1933.

globin content in patient 1, in spite of the fact that she apparently retained none of the administered iron. It will be noted also that the increase in hemoglobin in patients 3 and 4 accounted for more iron than was actually retained by the patients during the period of observation. Patient 3 retained 0.205 Gm of iron but used approximately 0.516 Gm in the building of hemoglobin, patient 4 retained 0.201 Gm but used 0.372 Gm in the formation of hemoglobin. This excess of hemoglobin iron above the retained iron must be obtained from the reserve supplies of the body and is in keeping with previous experimental work showing that copper aids in the mobilization and utilization of iron without actually increasing the absorption.¹⁷ Heath, giving iron parenterally but without additional copper, also noted a utilization of over 100 per cent in certain cases. In patients 5 and 6 only 3 and 9 per cent, respectively, of the retained iron was utilized, which is a no greater retention than when iron in the same amount is given alone.

TABLE 6—*Retention and Utilization of Iron*

Patient	Total Iron Intake, Gm	Total Iron Retained, Gm	Original Hemoglobin Value, Gm per 100 Cc	Average Daily Increase in Hemo globin, Gm per 100 Cc	Total Increase in Hemo globin, Gm per 100 Cc	Iron, Percentage Retained	Iron Percentage Utilized in Hemoglobin
1	4.259	-0.162	6.52	0.041	37.5	0.0	
2	5.762	1.049	8.15	0.067	81.0	18.1	4.2
3	5.733	0.205	4.36	0.143	172.0	3.5	9.0
4	5.816	0.201	6.20	0.103	124.0	3.4	6.8
5	5.119	3.594	5.59	0.071	43.0	70.2	2.5
6	24.849	8.741	4.78	0.110	265.7	35.1	3.2
7	5.038	0.962	5.59	0.040	36.0	19.0	2.1
8	6.799	1.256	7.54	0.047	57.0	18.4	2.5
9	8.229	2.566	6.14	0.131	196.5	31.1	7.1
10	11.228	1.483	2.23	0.114	239.2	13.2	6.8

LIVER FRACTION

The effect of a liver fraction on the retention of iron is illustrated by patients 7 to 10. These patients received the liver preparation in such amounts that the intake of iron ranged from 263.9 to 283.4 mg per day. The amount retained is shown in table 4. It will be noted that in patients 8 to 10 there was one period in which there was a decidedly negative iron balance but this did not come in the same balance period for the different patients as was true for the patients receiving copper. In table 5 will be found the average daily retention of iron of each patient, and this may be compared to the retention in other groups of patients receiving similar amounts of iron. It will be noted that the amount of iron retained is almost the same in those receiving liver and iron as in those receiving a smaller amount of iron alone and that both of these groups retained much more iron than

¹⁷ Elvehjem⁴ Cook and Spilles⁵ Mills⁶

did those patients receiving additional copper. The percentage of iron retained was larger in the patients receiving liver than in those who received copper, but it was smaller than in those receiving iron alone. The percentage of the iron utilized in the formation of hemoglobin was 4.5 per cent.

COMMENT

The results of these experiments indicate that when iron is given in moderate amounts (217 to 260 mg. per day), the addition of copper causes a diminished retention of iron. In spite of the small amount of iron retained, there is a satisfactory hemoglobin response, which in three of the four patients accounted for more iron than was retained by the body. This suggests that copper in some way aids in the utilization and mobilization of the available iron already stored in the body. When larger amounts of iron are administered in combination with copper (patients 5 and 6), there is no appreciable change in the retention or utilization of iron as compared to that in patients^{14b} receiving a similar amount of iron alone.

The combination of iron and a liver fraction produced a retention of iron which was slightly less than that in patients receiving iron alone. The percentage of iron retained dropped from 29.9 to 20.4 with the addition of liver. These results indicate that both the liver fraction and the copper diminish the amount of iron retained by the body but that the greater decrease is caused by copper.

The average daily increase in the hemoglobin content was 0.111 Gm. per hundred cubic centimeters of blood with iron alone, 0.089 Gm. with copper and iron and 0.082 Gm. with a combination of a liver fraction and iron. A somewhat smaller amount of iron was being administered in the first instance. These experiments were designed primarily for the study of the retention of iron, and results of the formation of hemoglobin based on so small a series of patients does not justify extensive and final conclusions. They suggest, however, that the addition of copper or a liver fraction does not increase the rapidity of the formation of hemoglobin in hypochromic anemias which are essentially post-hemorrhagic in origin.

SUMMARY

Iron balances were determined for ten patients with hypochromic anemia in order to study the effect of copper and liver extract on the retention of iron.

When iron was given in moderate amounts, the addition of copper led to a diminished retention but an increased utilization of iron. When the iron was administered in large doses, the effect of copper was negligible. Liver extract caused a slightly reduced retention of iron.

The increase in hemoglobin in this series of patients was no more rapid with the addition of copper or liver extract than with iron alone.

DIVERTICULUM OF THE PERICARDIUM

FURTHER DATA SHOWING PRESENCE OF EXTRATHORACIC ABSCESS

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AND

ALAN MORITZ, M D

CLEVELAND

In the January 1937 issue of the ARCHIVES was given a detailed report¹ of a patient with a mass which was considered to be a pericardial diverticulum. Further data are presented here.

The patient had been in good health and had been working as a night watchman. He was readmitted to the Lakeside Hospital in January 1937. Ten days previously there had been hematemesis of about 500 cc, and he had remained in bed at home for a week. Three days before admission to the hospital he had a head cold, and the night before entry fever, shortness of breath and pain in the chest were noted. When admitted to the hospital he had a temperature of 40 C (104 F). There were râles at the base of each lung. Cultures of the blood and sputum contained type II pneumococci. The patient died the next day.

Postmortem Examination (Dr Alan R. Moritz).—An autopsy was performed on January 22, four hours after the patient's death. The pathologic diagnoses were:

Chronic tuberculous pericarditis, with anterior extrathoracic pseudo-diverticulum (communicating abscess) of the pericardium.

Chronic cardiac compression, with extreme cardiac deformity.

Generalized chronic passive hyperemia.

Bronchopneumonia of the lower lobe of each lung.

Extensive fibrous pleural adhesions on the right.

Chronic peptic ulcer in the lesser curvature of the stomach, near the pylorus.

Hemorrhoids.

The fluctuant area beneath the skin of the right side of the thorax measured 4 cm in diameter, and its apex was elevated about 2.5 cm above the level of the adjacent wall of the chest (fig 1). On section an encapsulated abscess, containing about 5 cc of thin cloudy brown fluid, was noted beneath the origin of the pectoralis major muscle. The capsule was thick and was comprised of a dense lamella of fibrous connective tissue in the outer portion of which bundles of skeletal muscle were incorporated. The lining of the abscess was irregularly granular and was roughened by friable masses of necrotic tissue and organized exudate. The cartilage of the fourth rib had been destroyed, and through the defect the abscess communicated by means of a narrow sinus tract with an intra-

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1 Cushing, E. H. Diverticulum of the Pericardium, Arch Int Med 59:56 (Jan) 1937.

pericardial abscess (fig 2A) This abscess lay over the anterior basal portion of the heart, measured 15 cm in its greatest diameter and contained about 350 cc of thin cloudy brown fluid, in which were a number of delicate yellow crystals Near the ostium of the sinus in the pericardial abscess was a polypoid mass of granulation tissue that could have acted as a valve, permitting the entrance of fluid or gas into, but interfering with its passage out of, the pericardium

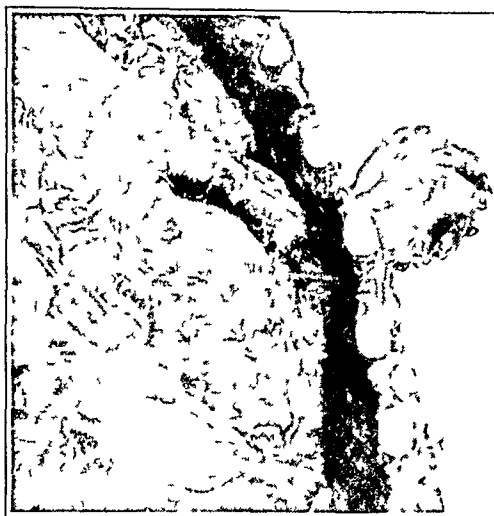


Fig 1—The thoracic contents and the extrathoracic abscess (pseudodiverticulum of the pericardium) viewed from the right side The right pleural cavity and the mediastinum have been obliterated by dense fibrous adhesions

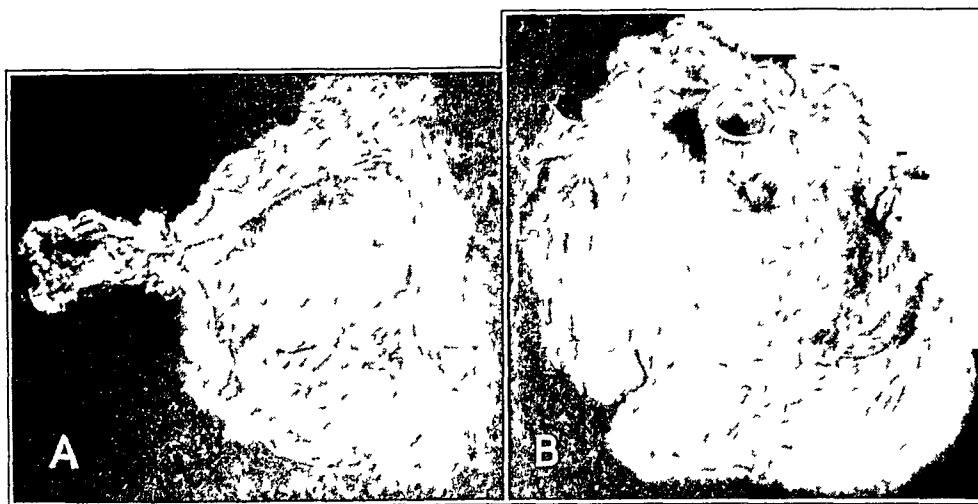


Fig 2—A, a view of the intrapericardial abscess, the sinus tract and the communicating extrathoracic abscess B, all the parietal and most of the visceral pericardium has been dissected from the heart The amount of compression of the heart is indicated by the concave deformity of the base, with extreme flattening of the auricles and the pulmonary conus

Posteriorly, laterally and inferiorly the pericardial sac was obliterated by dense fibrous adhesions in which were many thick plaques of calcareous material The inner surfaces of these plaques were irregularly nodular, with extension into

the underlying myocardium. An almost continuous band of calcareous material occupied the auriculoventricular sulcus.

Microscopic examination of the parietal pericardium and the wall of the communicating extrathoracic abscess revealed active solitary and active conglomerate tubercles. A section which included the transition between the parietal pericardium and the wall of the extrathoracic abscess showed an abrupt interruption of the orderly arranged lamellae of tissue of the parietal pericardium at the sinus. In their place the wall of the sinus and that of the extrathoracic abscess was comprised of a thick layer of organizing granulation tissue bearing no structural resemblance to the parietal pericardium, although being in direct continuity with it.

The heart, which was not enlarged, was greatly flattened in its anteroposterior axis, the flattening being most pronounced at the base (fig 2 B). The auricular appendages were obliterated, and the auricles were converted into thin hollow plates, the anterior and posterior walls of which approximated each other closely. The entire heart was surrounded by dense fibrous connective tissue, and both the inferior and the superior vena cava were compressed by scar tissue. The superior vena cava had a rather sharp posterior angulation in addition to the compression. The endocardium, valves and coronary arteries showed no significant changes.

The lungs were the seat of edema and chronic passive hyperemia, and there were small moist gray consolidated patches in the lower lobe of each lung. The right pleural cavity was obliterated by fibrous adhesions. There was no gross or microscopic evidence of active or healed tuberculosis of the lungs or mediastinal lymph nodes.

The remainder of the postmortem examination disclosed no significant changes other than chronic passive hyperemia of the liver, spleen, kidneys and gastrointestinal mucosa, hemorrhoids and a chronic peptic ulcer near the pylorus.

COMMENT

The route by which the tubercle bacilli reached the pericardium was not disclosed by the autopsy. No active or healed lesions of tuberculosis were discovered except those in the pericardium and in the communicating extrathoracic abscess. The possibility of primary pulmonary tuberculosis was not excluded, however, as roentgenograms of the lungs and mediastinal lymph nodes were not made. Although the cartilage of the fourth rib had been destroyed, there was no osteomyelitis of the ribs or sternum. The exact mode by which the communicating abscess developed was not disclosed. It may have resulted from a tuberculous mediastinal abscess which perforated externally beneath the pectoralis major muscle and internally into the pericardium. It is equally possible that a pericardial abscess may have perforated anteriorly, with destruction of the overlying costal cartilage and extension beneath the pectoral muscle. In either event the extrathoracic abscess was not a true pericardial diverticulum. The parietal pericardium ended abruptly at the beginning of the sinus tract.

The polypoid mass of granulation tissue, just at the mouth of the opening of the sinus into the pericardial abscess, was of such a character and so located as to account for the fact that air could be forced from the extrathoracic abscess into the pericardium, but having entered the pericardium it became trapped there.

It is surprising that there was so little clinical evidence of cardiac compression. The deformity of the auricles was extreme, and the entire heart was encased in a thick, extensively calcified mass of scar tissue. Although there were no ascites, the chronic passive hyperemia of the abdominal viscera constituted postmortem evidence of long-standing circulatory failure that was not apparent in life.

CALCIFICATION OF MYOCARDIUM WITH BONE FORMATION

REPORT OF A CASE

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AND

HARRY S LEVINE, M D

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A review of the literature discloses that calcification of the myocardium with bone formation is an extremely rare phenomenon. We have been able to find reports of only five cases. While heteroplastic bone formation in sclerotic arteries has been made the subject of investigation by Buerger and Oppenheimer¹ and Harvey,² no study has been made of calcification of the myocardium with bone formation. We believe, however, that if calcification of the heart is extensive enough to be demonstrated roentgenographically, ossification should be considered at the same time.

Calcification of the myocardium without bone formation has been mentioned in the following reports:

Scholz,³ in an extensive review of the literature up to 1924, referred to a total of thirty cases of myocardial calcification, adding a case of his own. He classified these into five groups:

- 1 Myocarditis, fourteen cases
- 2 Obliteration of coronary arteries, three cases
- 3 Sepsis, five cases
- 4 Calcium metastasis
 - (a) Involving endocardium only, two cases
 - (b) Combined with myocarditis, two cases
- 5 Direct extension from calcifying pericarditis, four cases

Diamond⁴ collected reports of fourteen additional cases of myocardial calcification, reporting at that time the case of an infant born pre-

Read before the Ocean Medical Society, Jan 18, 1937

From the Medical Service of Dr. Jacob N. Cohen, the Greenpoint Hospital

1 Buerger, L., and Oppenheimer, A. Bone Formation in Sclerotic Arteries, *J. Exper. Med.* **10** 354, 1908

2 Harvey, W. H. Experimental Bone-Formation in Arteries, *J. M. Research* **17** 25, 1907

3 Scholz, T. Calcification of the Heart. Its Roentgenologic Demonstration, *Arch. Int. Med.* **34** 32 (July) 1924

4 Diamond, M. Calcification of the Myocardium in a Premature Infant, *Arch. Path.* **14** 137 (Aug.) 1932

maturely, at 26 weeks, who died of cardiac failure thirty minutes after birth. The necropsy showed marked involvement of the right auricle and scattered deposits of calcium in the walls of both ventricles. The epicardium and the coronary vessels were not involved.

Moore⁵ cited the case of a white man aged 60 who, after having been hospitalized three times, was admitted a fourth time complaining of severe precordial pain and died six hours later. At autopsy the heart weighed 545 Gm, with the left ventricle bulging outward and containing a large deposit of calcium extending from the auriculoventricular groove downward to within 2 cm. of the apex.

Hirschboeck⁶ reported the case of a laborer 60 years of age in whom myocardial calcification occurred subsequent to coronary occlusion. The calcification involved the area of cardiac muscle supplied normally by the occluded descending branch of the left coronary artery. The anterior surface of the left ventricle was attached by tough fibrous adhesions to the anterior surface of the pericardial sac. The adherent part of the left ventricle showed extensive calcification. The anterior branch of the left coronary artery was partly obliterated.

Cutler and Sosman⁷ cited two cases in which there were extensive deposits of calcium in the myocardium, possibly caused by antecedent pericarditis and representing healed fibrinous pericarditis.

Microscopic evidence of bone formation in the calcified myocardium was not given in the aforementioned cases.

White⁸ has stated the opinion that in rare cases actual bone is found in the myocardium instead of mere masses of lime salts.

From the earlier literature may be mentioned reports by Bordenave,⁹ Simmons and Watson,¹⁰ Burns¹¹ and Renauldin¹² of cases of bone formation in the myocardium.

5 Moore, J. J. Myocardial Calcification, *Am J Roentgenol* **31** 766, 1934.

6 Hirschboeck, F. J. Calcification of Myocardium Following Coronary Occlusion, *Am Heart J* **10** 264, 1934.

7 Cutler, E. C., and Sosman, M. C. Calcification in the Heart and Pericardium, *Am J Roentgenol* **12** 312, 1924.

8 White, Paul D. Heart Disease, New York, The Macmillan Company, 1931.

9 Bordenave, M. A Case of Ossification of the Heart, *Mém Acad roy de sc*, Paris **1** 50, 1768, cited by Scholz.⁸

10 Simmons, S. F., and Watson, H. A Case of Ossification of the Heart, *Med Communications*, London **1** 228, 1783, cited by Scholz.³

11 Burns, Allan. Observations on Some of the Most Frequent and Important Diseases of the Heart, Edinburgh, Bryce & Co., 1809, p. 129.

12 Renauldin, M. Mémoire sur le diagnostic de quelques maladies organiques du coeur, *J de méd, chir, pharm* **11** 254, 1806, cited by Corvisart, J. N. *Essai sur les maladies et les lésions organiques du coeur et des gros vaisseaux*, ed 3, Paris, Méquignon-Marvis, 1818.

Topham¹³ observed a number of large sections of ossification in the myocardium of a man aged 61 years who suffered from cardiac insufficiency. He said

These hard and stony masses were found in the lines of the auricular-ventricular grooves. One, the larger, was 4 x 1 inch, widening up to 2 inches along the auricular-ventricular groove. In a similar position on the left side were 2 smaller fragments each about 1 x 1½ inches at their greatest diameters. The aorta and coronary arteries appeared normal. The heart was large, flabby and dilated. It had a firm fibrous covering which proved difficult to detach.

A patient with myocardial calcification with bone formation was observed at the Greenpoint Hospital, and since there is a paucity of material in the literature on this condition, we wish to present this report.

REPORT OF CASE

An Italian widower aged 64, a pedler, was admitted to the Greenpoint Hospital on Jan 17, 1933, where he died on February 18. His chief complaint was of abdominal distention. His family history was essentially unimportant. His personal history showed that he had been an excessive wine drinker since the age of 30, imbibing two or three bottles daily. He smoked from eight to ten Italian cigars a day. He married at 18 and had twelve children. He had been a strenuous worker all his life. He had no knowledge of any cardiac lesion, rheumatism or venereal infection. His past history revealed no serious illness or operation. Eight months previously he noticed a gradual and progressive enlargement of the abdomen associated with shortness of breath on exertion. He was admitted on two occasions to a hospital at the onset of his illness, at which time abdominal paracentesis offered little relief because of the rapid reaccumulation of fluid. When he came under our observation his abdomen was tremendously enlarged, and the slightest exertion produced marked dyspnea. He had no cough, hemoptysis or precordial pain. He had lost a great deal of weight and had become progressively weaker. He was constipated and had marked nocturia.

The patient was poorly nourished, pale and dyspneic and appeared acutely ill. He was not cyanotic. Pterygium was present bilaterally. The supraclavicular depressions were marked. There was no venous engorgement or increased arterial pulsation in the neck. The trachea was not fixed. Retraction of the intercostal spaces in the lower portion of the right and left axillary regions was marked. Flatness on percussion with distant breathing was noted at the base of each lung. The maximal precordial impulse was observed in the fifth left intercostal space, 2 cm outside the midclavicular line. Percussion revealed that the right and left cardiac borders together with the aortic arch were enlarged. The sounds were of fair quality and regular. A faint systolic murmur was audible over the apical and aortic areas. The aortic second sound was louder than the pulmonic second sound. No thrills or rubs were heard. The cardiac apex failed to shift with postural change. The abdomen was enormously distended, and shifting dullness together with a fluid wave was noted. The superficial veins in the lower portion of the chest and midabdominal area were markedly dilated. On compression they

13 Topham, J. A. Bone Formations in the Heart, *Brit. M. J.* 2: 953 (Oct 13) 1906.

filled from below. Edema was noted in the sacrum, scrotum, thighs and ankles. The extremities were warm and of good color and showed normal arterial pulsations. The external genitalia were normal. Rectal examination revealed slight enlargement of the prostate.

Abdominal paracentesis was performed on the day after the patient's admission to the hospital, and 5 gallons (23 liters) of yellowish opalescent fluid was obtained. This fluid proved to be a transudate. A smear of the fluid showed no malignant cells or organisms, a differential count showed 81 per cent polymorphonuclear cells and 19 per cent lymphocytes. After the paracentesis the liver was palpated 5 fingerbreaths below the right costal margin. It was firm and smooth. The spleen was not palpable. Peristalsis of the intestines at this time was visible. Subsequently, three additional paracenteses were performed because of the discomfort and dyspnea produced by the reaccumulation of ascitic fluid. A total of 14 gallons (64 liters) of ascitic fluid was obtained. After the second paracentesis, on the tenth day of hospitalization, the scleras became icteric. The skin was not jaundiced. The icteric index at this time was 38, a positive immediate direct van den Bergh reaction was obtained. Later the icteric index was 32.

The urine at all times showed the presence of bile and an increase in urobilinogen, together with a faint trace of albumin. The kidneys showed ability to concentrate. The blood count showed erythrocytes, 3,050,000 and leukocytes, 12,000, with 73 per cent polymorphonuclears and 27 per cent lymphocytes. The hemoglobin value was 60 per cent. The total urea content of the blood was 35 mg. The Wassermann reaction was negative. The stools showed occult blood on numerous examinations.

The blood pressure never rose above 110 systolic, the diastolic pressure remained in the 70's. The temperature ranged between 99 and 101 F, the pulse rate, between 90 and 100, and the respiratory rate, between 30 and 36.

During his stay in the hospital the patient grew progressively worse and refused to take nourishment. He became stuporous and lapsed into coma on February 17, with pulmonary edema. He died the next day.

Roentgenographic studies of the chest revealed unusual and interesting findings. The pulmonary fields showed an increase in hilar calcification but no infiltration or consolidation. Figure 1*A* shows the heart to be considerably enlarged in all diameters, with a large circular opacity in the lower aspect of the left field extending above the level of the diaphragm for about 2 inches (5 cm), this opacity did not extend to the outer aspect of the pulmonary field, the periphery showed calcification. The left costophrenic sinus appeared clear. The transverse diameter of the aortic arch was increased. The mediastinal shadow was increased to the right in the middle and lower thirds, this was probably due to dilatation of the right auricle or the descending aorta. The right and left diaphragmatic domes were well outlined at the usual levels. An oblique view (fig 1*B*) shows the calcified tissue to be anteriorly situated, thus excluding aortic aneurysm with calcification. Fluoroscopy and further roentgen examinations showed diffuse widening of the aorta and concentric hypertrophy of the left ventricle. Contractions in the region of the left ventricle were not observed on fluoroscopy. At no time was calcification thought to be present in the pericardium. In order to determine the extent of calcification more accurately, a roentgenogram of the excised heart was made (fig 2). Here one may see the calcification involving the entire left ventricle, with a denser area containing bone. The electrocardiogram (fig 3) revealed myocardial damage.

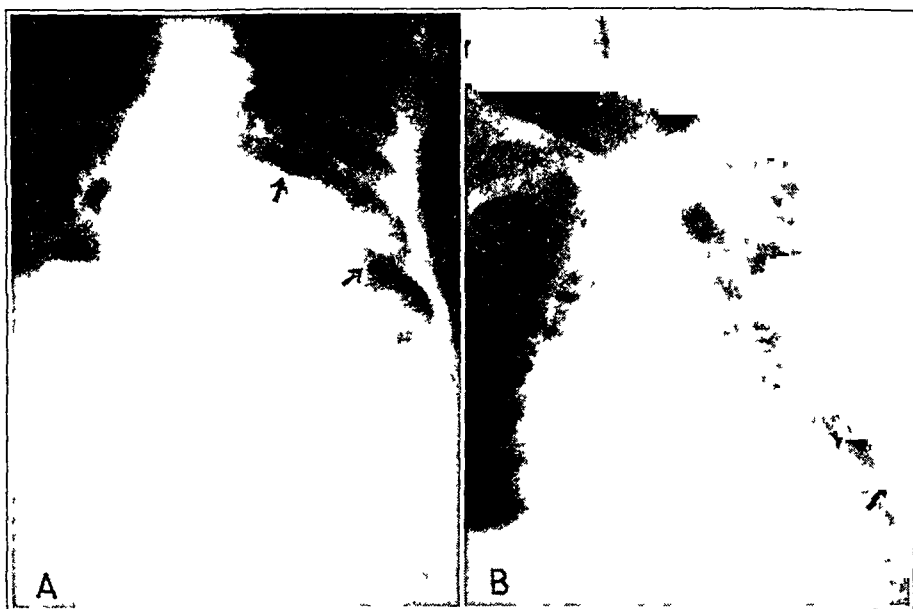


Fig 1—*A*, teleoroentgenogram showing the heart enlarged in all diameters, with a large circular opacity in the lower aspect of the left field. The periphery of this opacity showed calcification. *B*, an oblique view showing the calcified tissue to be anteriorly situated.



Fig 2—Roentgenogram of the excised heart, showing the extent of the bone formation in the left ventricle.



Fig 3—Electrocardiogram showing severe myocardial damage



Fig 4—Left ventricle exposed, showing the oval shape and the thinning of the wall, with bone formation

The anatomic diagnosis at postmortem examination was aneurysm of the left ventricle, severe sclerosis of the coronary vessels, myocardial calcification of the left ventricle, arteriosclerotic aortitis with ulcerations, anterior and lateral pericardial adhesions, pleural effusion with adhesions, fibrosis of the spleen and pancreas, severe cirrhosis and infarctions of the liver and passive congestion of the viscera. The kidneys showed evidence of chronic nephritis.

The heart weighed 800 Gm and was enlarged to the right and left (fig 4). The left ventricle was oval, and its distal three-fifths was transformed into a

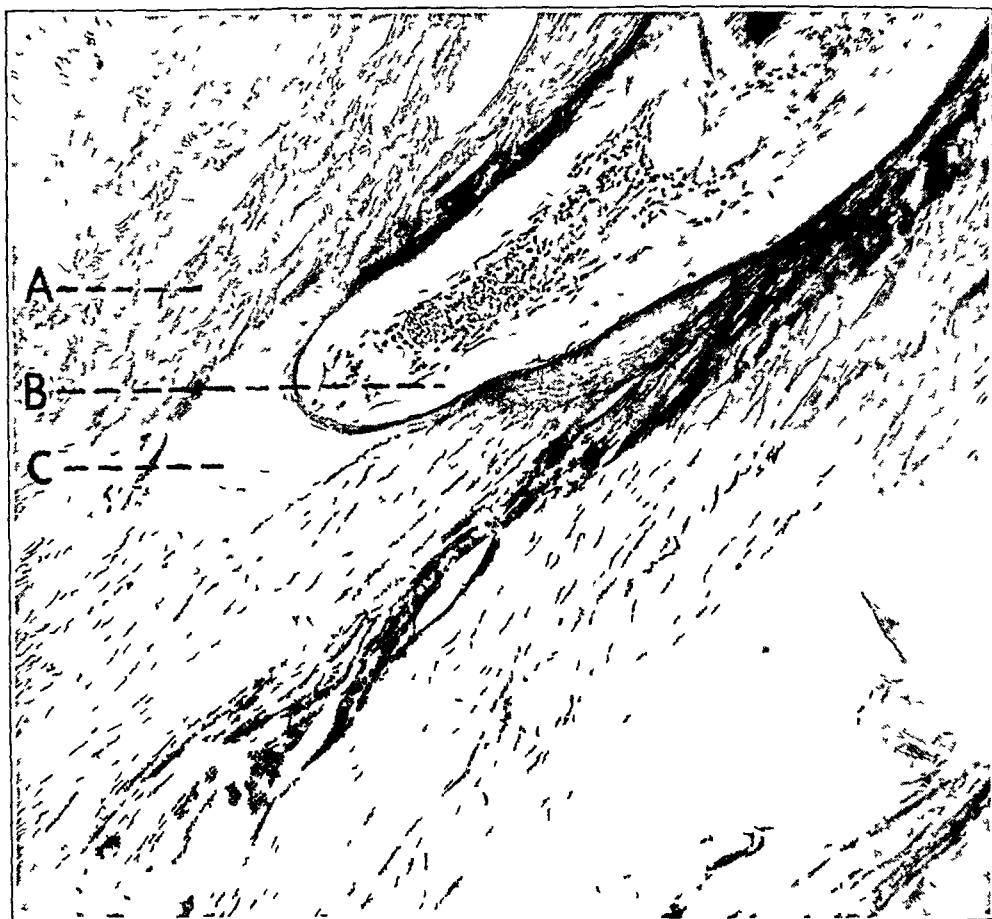


Fig 5—Microscopic section ($\times 40$) showing *A*, fibrous tissue, *B*, marrow space containing fat globules, blood cells and capillaries, and *C*, osseous trabeculae

large aneurysm about the size of a fist. The aneurysmal wall was thin, measuring from 2 to 8 mm in thickness, it showed diffuse calcification, bulged outward and to the right and caused marked compression and narrowing of the right ventricle. The remaining myocardium of the left ventricle was about 2 cm thick and pale, it showed diffuse areas of fibrosis. All the valves were apparently normal except for some fibrous thickening of the free edge of the mitral valve. The anterior descending branch of the left coronary artery showed marked sclerosis, with an eccentric lumen in the upper third, the distal two thirds of the lumen was completely obliterated. The posterior descending branch of the right

coronary artery was tortuous and sclerotic. The lumen was narrowed. The pericardial sac contained a small amount of clear fluid and was partly obliterated. The pericardium was adherent to the anterior lateral aspect of the left ventricle.

Microscopic study of a section of the myocardium in the region of the aneurysm (fig 5) showed scar tissue with calcification and ossification, together with the formation of true marrow spaces in which all the cells usually found in bone marrow were represented.

The diagnosis was myocardial calcification with histologic evidence of bone formation.

Dr Rosa Aronoff, pathologist, analyzed the pathologic material, and Dr Leroy P. Van Winkle, roentgenologist, interpreted the roentgenograms.

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THERAPEUTIC VALUE OF CONVALESCENT SERUM IN SCARLET FEVER

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AND

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MILWAUKEE

The Milwaukee Convalescent Serum Center, in the Columbia Hospital, since its establishment in February 1935 has made pooled human convalescent serum available for use in the prevention and treatment of various contagious diseases. The largest demand has been for serum from persons convalescent from scarlet fever, although there have been calls also for measles, mumps, acute poliomyelitis, chickenpox and normal serum.

The method of collecting, preparing and dispensing serum from patients convalescent from scarlet fever has been described,¹ and the methods of administration, the amounts recommended and the preliminary results have been discussed.² Further results obtained with the serum have been recorded through the use of follow-up cards sent to physicians who cared for the patients to whom the serum was given. The response to the questionnaire has been excellent. Only 29 of the 333 questionnaires sent out for information on the therapeutic results of scarlet fever serum remain unanswered. Another 10 were answered in an unsatisfactory manner.

This study is a comparison of the data for a total of 1,028 patients with scarlet fever, 139 of whom received the commercial antitoxin, 589 of whom received human convalescent serum and 300 of whom received neither antitoxin nor immune serum. All except 294 patients who received convalescent serum at home were treated in South View Hospital, the Milwaukee city isolation hospital.

The sex and average age incidence were approximately the same for all the groups. The majority (60.2 per cent) of patients treated at home had mild or moderately severe scarlet fever, whereas, among

Presented in abstract form before the Central Society for Clinical Research, Chicago, Nov 7, 1936

1 Hardgrove, M. The Milwaukee Convalescent Serum Center, Minnesota Med **18** 541-542 (Aug) 1935

2 Hardgrove, M. The Use of Human Convalescent Serum in Infectious Diseases, Wisconsin M J **34** 812-816 (Nov) 1935

the patients in the hospital 100 per cent of those who received antitoxin and 95 per cent of those who received convalescent serum were severely ill or had complications. Neither of these serums was used in the routine treatment of patients with scarlet fever in the hospital.

Most (83 per cent) of the patients in the hospital were admitted before the fifth day of illness. The majority (79.3 per cent) of those who were cared for at home received convalescent serum within three days after the onset of the disease. The average length of time until a permanent normal temperature was reached after treatment was twelve and four-fifths days for the patients in the hospital who received antitoxin, four and one-half days for those in the hospital who received convalescent serum and only one and three-fifths days for those receiving convalescent serum at home. The patients in the control group reached a normal temperature on an average of ten and nine-tenths days after admission to the hospital. In this group were many patients with mild scarlet fever, which lowered the average length of time before a normal temperature was reached.

The average twelve hour fall in temperature for patients receiving convalescent serum was 3.5 F, as compared with 2.1 F for those who were given antitoxin.

A satisfactory response was shown by 68.4 per cent of those treated at home who were given serum within a three day period and by 14.9 per cent of those who were given serum later than three days after the onset of the disease, making a total of 83.3 per cent. In 90 per cent of the hospital group a satisfactory response was observed after the use of convalescent serum, whereas only 60 per cent responded satisfactorily to antitoxin.

After the treatment was given complications persisted or new ones appeared in 35 per cent of those who received antitoxin treatment, 16 per cent of the hospital group and 12 per cent of those who received convalescent serum at home. These results compare favorably with those of Hoyne, Levinson and Thalhimer,³ who showed that the incidence of complications was reduced approximately one-half through the early use of the serum.

The incidence of reactions after the use of convalescent serum was only 1 per cent, as opposed to 35 per cent after the use of commercial antitoxin. The early reactions noticed after the use of convalescent serum were transitory increases in temperature, chills and articular pains. Mild urticaria occasionally occurred within twenty-four hours.

3 Hoyne, A. L., Levinson, S. O., and Thalhimer, W. Convalescent Scarlet Fever Serum. Its Prophylactic and Therapeutic Value, a Review of 2,875 Cases, *J. A. M. A.* **105** 783-789 (Sept. 7) 1935.

or two or three weeks later. The reactions did not seem to interfere with the beneficial effect of the serum, nor were they severe enough to cause serious concern. The reactions of immediate occurrence call attention to the fact that certain precautions should be taken when the serum is given. The serum should be warmed to body temperature in a water bath, overheating will coagulate the serum and make it unfit for use. The serum should be injected slowly, an all glass syringe that has been carefully cleaned and sterilized being used. More prompt results are obtained by intravenous therapy, but the precautions must be strictly observed.

The average dose given the patients treated at home was 33.6 cc. The individual doses ranged from 10 to 100 cc. The average dose of

Therapeutic Value of Convalescent Serum in Scarlet Fever

	Hospital Group			Home Group
	Control	Antitoxin	Convalescent Serum	Convalescent Serum
Number of patients (total, 1,028)	300	139	295	294
Severe or complicated scarlet fever	57%	100%	95%	39.8%
Patients ill less than 5 days before hospitalization	83%	99%	87%	Less than 3 days, 79.3%
Average time until normal temperature was reached after admission to hospital	10.9 days	15.3 days	9.2 days	From onset of illness 4.25 days
Average time until normal temperature was reached after treatment		12.8 days	4.58 days	1.66 days
Average 12 hour drop in temperature		2.1 F	3.5 F	3.4 F
Satisfactory response		60%	90%	First 3 days, 68.4%, after 3 days, 14.9%, total, 83.3%
Complications following treatment		35%	16%	12.9%
Reactions		35%	1%	1%
Deaths	6 (2%)	4 (2.8%)	8 (2.7%)	5 (1.7%)

convalescent serum given in the hospital was 32.7 cc., with a range of from 20 to 80 cc. per injection. In some cases these doses were repeated.

Park⁴ found the mortality rate to be 2.8 per cent for 569 hospitalized patients with scarlet fever, 40 of whom received antitoxin. The groups discussed here are perhaps too small to warrant a comparison of the mortality rates, but it may be noted that the rate was much less for those treated at home (1.7 per cent). It must be remembered that only the very sick patients received convalescent serum or antitoxin in the hospital.

It is difficult to express statistically the satisfaction obtained in treating the scarlet fever patient with convalescent serum. In the

⁴ Park, W. H. Scarlet Fever. Etiology, Prevention by Immunization, and Antitoxic Treatment, J. A. M. A. 85:1180-1186 (Oct. 17) 1925.

majority of patients the results, as noted at the bedside, are striking. The higher the temperature and the more toxic the patient's condition, the better the results if the serum is given early. As a rule, after an intravenous injection has been given early to a patient with uncomplicated scarlet fever, his mind clears, the vomiting ceases, the appetite returns and the temperature and pulse rate begin to fall. Within from twelve to eighteen hours a patient who has been delirious and very sick will usually be convalescing. If the serum is given late in the disease or after complications have already set in, larger and repeated doses are often necessary.

The use of serum of patients convalescent from scarlet fever is to be encouraged in associated infections thought to be due to a (beta) hemolytic streptococcus⁵. Scarlet fever serum has been of value in the treatment of the erysipelas which appears as a result of contact with scarlet fever⁶. Improvement has also been noted as a result of its use in "surgical scarlet fever," following an operation or childbirth.

CONCLUSIONS

In a comparison of the results obtained in 139 patients with scarlet fever treated with commercial antitoxin, 589 treated with pooled human serum of patients convalescent from scarlet fever and 300 receiving neither but who received the same general symptomatic treatment, the most satisfactory results were observed after the use of convalescent serum.

When serum was given early in adequate doses, there was an apparent decrease in the mortality rate, as well as a reduction in the complications. As a rule, all the symptoms improved, and there was a marked reduction in the length of time until the temperature reached normal.

Serious untoward reactions following the use of human convalescent serum, given either intramuscularly or intravenously, have not been noted.

Excellent response has been obtained on the part of the physicians. It is through their cooperation that it is possible to estimate the value of this therapeutic agent among private patients treated at home.

5 Thalhimer, W., and Levinson, S. O. Pooled Convalescent Scarlet Fever Treatment of Diverse Streptococcal Infections, *J. A. M. A.* **105** 864-866 (Sept 14) 1935.

6 Fox, M. J. The Biological Relationship Between Erysipelas and Scarlet Fever, *Wisconsin M. J.* **35** 797-801 (Oct) 1936.

INCREASED URINARY EXCRETION OF IODINE IN HYPERTHYROIDISM

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Recently we¹ presented our findings concerning the normal urinary iodine of man, together with a review of the pertinent literature. At present few data² concerning the urinary loss of iodine in hyperthyroidism are available. These reveal a pathologic increase in the urinary excretion of iodine in certain patients with hyperthyroidism. We therefore became interested in making a more extensive investigation of this particular problem in order to determine significant variations from normal in the daily urinary loss of iodine of hyperthyroid patients.

Phillips and one of us (G M C)^{2a} observed in 1932 an increased urinary loss of iodine during certain phases of hyperthyroidism. Since that time others³ have reported their investigations on patients with hyperthyroidism. The latter findings, on the whole, confirm the earlier ones^{2a, b}. Our purpose in the present communication is to report an extensive investigation of the renal excretion of iodine of forty patients with hyperthyroidism studied over a total period of two hundred and ninety-eight days.

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1 Curtis, G M, Puppel, I D, Cole, V V, and Matthews, N L. The Normal Urinary Iodine of Man, *J Lab & Clin Med* **22** 1014, 1937

2 (a) Curtis, G M, and Phillips, F J. The Urinary Excretion of Iodine, *J Clin Investigation* **12** 963, 1933. (b) Scheffer, L. Jodstoffwechsel bei Schilddrüsenerkrankungen, *Klin Wchnschr* **12** 1285 (Aug 19) 1933. (c) Curtis, G M, and Phillips, F J. The Urinary Excretion of Iodine in Toxic Goiter, *J A M A* **101** 1992 (Dec 16) 1933. (d) Szasz, E. Ueber Jodausscheidung gesunder und hyperthyreoter Menschen im Hohenklima, *Med Klin* **29** 1584 (Nov 17) 1933. (e) Elmer, A, and Scheps, M. The Iodine Content of Blood and of Urine and the Basal Metabolic Rate. Their Value in the Diagnosis of the Function of the Thyroid Gland, *Acta med Scandinav* **82** 126, 1934. (f) Scheffer, L. Ueber die Rolle des Jods bei der Entstehung von Schilddrüsenerkrankungen, *Schweiz med Wchnschr* **64** 969 (Oct 20) 1934. (g) Jodstoffwechsel bei Hyperthyreosen, *Klin Wchnschr* **13** 1570 (Nov 3) 1934. (h) Scheffer, L, and von Megay, L. Jodstoffwechsel bei Kropfträgern, *ibid* **14** 1360 (Sept 21) 1935. (i) Elmer, A, and Scheps, M. La thyroxine est-elle éliminée par les reins chez l'homme normal et chez les basodowiens? *Compt rend Soc de biol* **115** 968, 1934.

3 Scheffer^{2b} Szasz^{2d} Elmer and Scheps^{2e} Scheffer^{2f, g} Scheffer and von Megay^{2h} Elmer and Scheps²ⁱ

METHODS

The ward and laboratory methods were essentially similar to those presented in a previous report¹ The patients were all investigated preoperatively They did not receive thyroid therapy or any form of iodine medication for at least two weeks previous to or during this study The daily diets were of high caloric value Foods of known high iodine content,⁴ particularly sea foods, were excluded The early analyses of the iodine of the blood and urine were all made by the method of Phillips and one of us (G M C)⁵ Others were made by the Matthews⁶ modification of the Leiper⁷ procedure

OBSERVATIONS

The forty patients all presented the characteristic clinical picture of hyperthyroidism, and the diagnosis was confirmed after extensive observation and investigation Their ages varied from 14 to 57 years Thirty-three were females, and seven were males They presented no other recognized abnormality, such as evidence of renal damage, which might so far as is known affect iodine metabolism The forty patients were divided into three groups, those with exophthalmic goiter, toxic nodular goiter and unusual forms of hyperthyroidism

EXOPHTHALMIC GOITER

The daily urinary excretion of iodine was determined over a total period of one hundred and ninety-nine days for twenty-four patients (table 1) with exophthalmic goiter Their ages varied from 14 to 48 years Eighteen were females and six were males These patients excreted daily from 29 to 730 micrograms of iodine in the urine, with averages ranging from 46 to 357 micrograms The grand average was 147 micrograms per twenty-four hours The average concentration of iodine in the urine was 12.3 micrograms per hundred cubic centimeters

The grand average basal metabolic rate was plus 54 per cent The rate was elevated in twenty-three patients and normal in one patient (table 1, patient 18) The average iodine content of the blood was greatly increased in twenty-one patients, slightly increased in one patient (table 1, patient 3) and normal in two patients (table 1, patients 6 and 15) The average daily urinary loss of iodine was increased in eighteen and normal in six patients (table 1, patients 3, 4, 7, 13, 19 and 22)

4 Cole, V. V., Curtis, G. M., and Bone, M. L. The Iodine Content of Hospital Foods, *J. Am. Dietet. A.* **10** 200, 1934

5 Phillips, F. J., and Curtis, G. M. The Clinical Determination of Iodine in Blood, Urine, and Feces, *Am. J. Clin. Path.* **4** 346, 1934

6 Matthews, N. L. To be published

7 Leiper, T. Die Bestimmung kleinster Jodmengen in organischem Material, *Biochem. Ztschr.* **261** 436, 1933, Zur Kenntnis des physiologischen Blutjodspiegels, *ibid.* **270** 448, 1934

One (approximately 4 per cent) of the twenty-four patients with exophthalmic goiter presented a normal basal metabolic rate (table 1, patient 18). However, there was a greatly increased urinary excretion of iodine. Two patients (approximately 8 per cent) showed a normal average content of blood iodine (table 1, patients 6 and 15). These revealed an elevated average basal metabolic rate and an increased urinary excretion of iodine. The six patients with a normal urinary

TABLE 1—*Urinary Loss of Iodine in Exophthalmic Goiter*

Date	Patient Number	Patient	Sex	Age	Basal Meta- bolic Rate, % Plus	Days of In- vestiga- tion	Average 24 Hour Urinary Volume, Cc	Average Urinary Concen- tration of Iodine, Micrograms per 100 Cc	Limits of Daily Urinary Excretion of Iodine, Micrograms		Average 24 Hour Urinary Excretion of Iodine, Micrograms
									Low	High	
Dec 1932	1	M F	F	35	42	2	950	19.9	103	214	161
Jan 1933	2	J B	F	32	19	5	1,115	14.9	55	165	106
March 1933	3	F M	F	18	37	13	2,635	2.6	34	122	64
April 1933	4	C W	M	38	54	20	950	9.5	29	186	69
May June '33	5	H C	F	17	18	8	805	28.9	87	257	173
June 1933	6	H L	F	37	91	7	1,125	10.0	36	233	117
July 1933	7	G M	F	25	88	1	570	8.1			46
Aug 1933	8	D S	F	51	109	4	1,370	14.9	133	253	206
Oct 1933	9	M W	F	25	64	4	1,060	14.5	92	225	176
Oct 1933	10	J P	M	48	84	4	1,945	12.6	74	395	251
Oct 1933	11	F P	M	39	47	4	1,835	7.7	83	213	134
Nov 1933	12	R D	F	37	75	4	1,045	21.5	101	401	241
April 1934	13	T F	F	24	28	15			44	63	52
Nov 1934	14	R S	F	24	79	14	1,235	12.1	68	256	131
Feb 1935	15	E T	F	21	52	1	780	22.7			178
June 1935	16	R B	F	22	36	10	1,200	7.1	55	110	82
Oct Nov '35	17	S T	F	57	23	15	2,190	9.8	36	269	100
Oct Nov '35	18	C C	M	44	11	3	2,175	7.5	219	297	245
Dec 1935	19	V M	F	44	38	7	1,495	3.9	29	102	59
Mar Apr '36	20	O C	M	35	61	10	1,575	13.2	110	258	194
April 1936	21	M W	F	14	29	3	1,490	14.2	186	246	209
June 1936	22	L W	F	19	49	19	1,350	4.5	35	97	60
July Aug '36	23	L A	F	22	62	7	1,730	8.0	71	181	123
July Aug '36	24	F W	M	23	92	19	2,475	15.7	148	730	357
Grand averages					54	8.3	1,440	12.3			147
Low and high limits of daily urinary excretion of iodine									29	— 730	46—357

iodine content showed an elevated average basal metabolic rate and an increased average blood iodine content. Gross and microscopic examination of the goitrous tissue removed at operation confirmed the diagnosis of exophthalmic goiter in each case.

The highest urinary excretion of iodine (730 micrograms) for this series of patients with exophthalmic goiter occurred in a patient (table 1, patient 24) presenting a greatly increased energy metabolism and the exaggerated clinical features characteristic of an impending crisis of hyperthyroidism. Subsequent partial amelioration of the symptoms was accompanied by a lowering (to 148 micrograms per day) of the increased urinary iodine.

TOXIC NODULAR GOITER

There were nine patients (eight women and one man) with toxic nodular goiter. These (table 2) were investigated over a total period of forty-eight days. The ages varied from 22 to 56 years. These patients excreted daily from 31 to 954 micrograms of iodine in the urine, with averages of from 39 to 593 micrograms. The grand average was 214 micrograms per twenty-four hours. The grand average concentration of iodine in the urine was 20 micrograms per hundred cubic centimeters.

The grand average basal metabolic rate was plus 21 per cent. It was elevated in eight patients and normal in one patient (table 2, patient 6). The average value for blood iodine was increased in eight patients and normal in one patient (table 2, patient 2). The average

TABLE 2—*Urinary Loss of Iodine in Toxic Nodular Goiter*

Date	Patient Number	Patient	Sex	Age	Basal Metabolic Rate, % Plus	Days of Investigation	Average 24 Hour Urinary Volume, Cc	Average Urinary Concentration of Iodine, Micrograms per 100 Cc	Limits of Daily Urinary Excretion of Iodine, Micrograms		Average 24 Hour Urinary Excretion of Iodine, Micrograms
									Low	High	
Jan 1933	1	B N	F	22	16	5	945	6.2	51	73	64
Feb 1933	2	D R	F	27	18	3	425	46.7	85	276	201
Feb 1933	3	C C	F	31	19	5	1,780	15.1	196	314	269
Aug 1933	4	L M	F	24	18	3	1,235	31.5	282	448	377
July 1935	5	P B	F	44	42	10	1,360	47.1	181	954	593
Nov 1935	6	C H	F	54	0	5	835	11.5	69	111	90
Dec 1935	7	E S	M	52	22	10	1,405	2.8	31	64	39
Jan 1936	8	M H	F	36	24	1	1,690	9.5			161
Jan 1937	9	S W	F	53	21	3	1,265	10.4			132
Grand average					20	5.3	1,215	20.1			214
Low and high limits of daily urinary excretion of iodine									31	— 954	39—593

daily urinary excretion of iodine was greatly increased in six patients, slightly increased in one patient (table 2, patient 6) and normal in two patients (table 2, patients 1 and 7).

One patient (approximately 11 per cent) showed a normal basal metabolic rate (table 2, patient 6). However, there was an increased content of iodine in the blood and urine. Another (approximately 11 per cent) showed a normal value for blood iodine (table 2, patient 2). The basal metabolic rate was only slightly elevated, however, the urinary excretion of iodine was greatly increased. Two patients (approximately 22 per cent) disclosed a normal average urinary excretion of iodine (table 2, patients 1 and 7). The basal metabolic rate was slightly increased in one patient (table 2, patient 1) and plus 22 per cent in the other (table 2, patient 7). The value for blood iodine was increased in both.

UNUSUAL FORMS OF HYPERTHYROIDISM

Two patients with mixed goiter (table 3) showed an elevated basal metabolic rate, an increased blood iodine content and an increased urinary excretion of iodine. A patient with carcinoma of the thyroid gland (table 3) revealed an elevated basal metabolic rate, a normal value for blood iodine and an increased urinary excretion of iodine. A patient with induced hyperthyroidism, investigated immediately after the cessation of excessive thyroid medication (table 3), revealed an elevated basal metabolic rate, a definitely increased blood iodine content and a greatly increased urinary excretion of iodine. Of the three patients having pseudorecurrent hyperthyroidism (table 3), patients E R and M R revealed an elevated basal metabolic rate and patient D B a normal

TABLE 3—*Urinary Loss of Iodine in Unusual Forms of Hyperthyroidism*

Type	Patient	Sex	Age	Basal Meta- bolic Rate, % Plus	Days of Inves- tiga- tion	Average 24 Hour Urinary Volume, Cc	Average Urinary Concen- tration of Iodine, Micro- grams per 100 Cc	Limits of Daily Urinary Excretion of Iodine, Micrograms		Average 24 Hour Urinary Excre- tion of Iodine, Micro- grams
								Low	High	
Mixed goiter	M H	F	33	49	7	1,235	40.8	405	628	483
Mixed goiter	M K	F	37	61	2	1,175	24.3	157	428	293
Carcinoma	F B	F	52	35	13	3,540	10.2	103	832	362
Induced hyperthy- roidism	E H	F	17	16	3	1,635	41.2	302	600	467
Pseudorecurrent hyperthyroidism*	E R	F	44	34	6	3,190	2.2	53	98	70
	M R	F	25	50	13	1,000	19.6	84	276	189
	D B	F	28	13	7	600	5.2	13	60	30

* Pseudorecurrent hyperthyroidism refers to recurrent hyperthyroidism following insufficient surgical removal of goitrous tissue or subsequent to removal of a single lobe.

rate. The blood iodine content was increased in patients M R and D B and normal in patient E R. The daily urinary excretion of iodine was increased in patient M R but normal in patients E R and D B.

COMMENT

Iodine is a normal constituent of human urine.¹ The daily physiologic fluctuation¹ in its excretion by the kidney may be great (chart). Two hundred and twenty-seven daily determinations of the urinary iodine content made for thirteen persons without evidence of thyroid disease gave a range of from 7 to 196 micrograms per twenty-four hour period, with averages of from 36 to 78 micrograms.¹ The grand average was 51 micrograms per twenty-four hour period. This daily fluctuation may be due to many normal variables which affect iodine metabolism, such as the qualitative and quantitative intake of iodine, the geographic region, the activity of the thyroid gland, the metabolism of the

thyroid hormone in the extrathyroid tissues, emotion and the excretion of iodine through other channels, such as the skin and the gastrointestinal tract. Nevertheless, normal persons maintained for days on a constant regimen⁸ (chart) show only a small range in the daily urinary output of iodine.

Pathologically, the greatest increase in the urinary excretion of iodine occurs in certain patients with hyperthyroidism, as revealed in tables 1 to 4. The grand average value for urinary iodine for these forty patients was 184 micrograms per day, which is between three and four

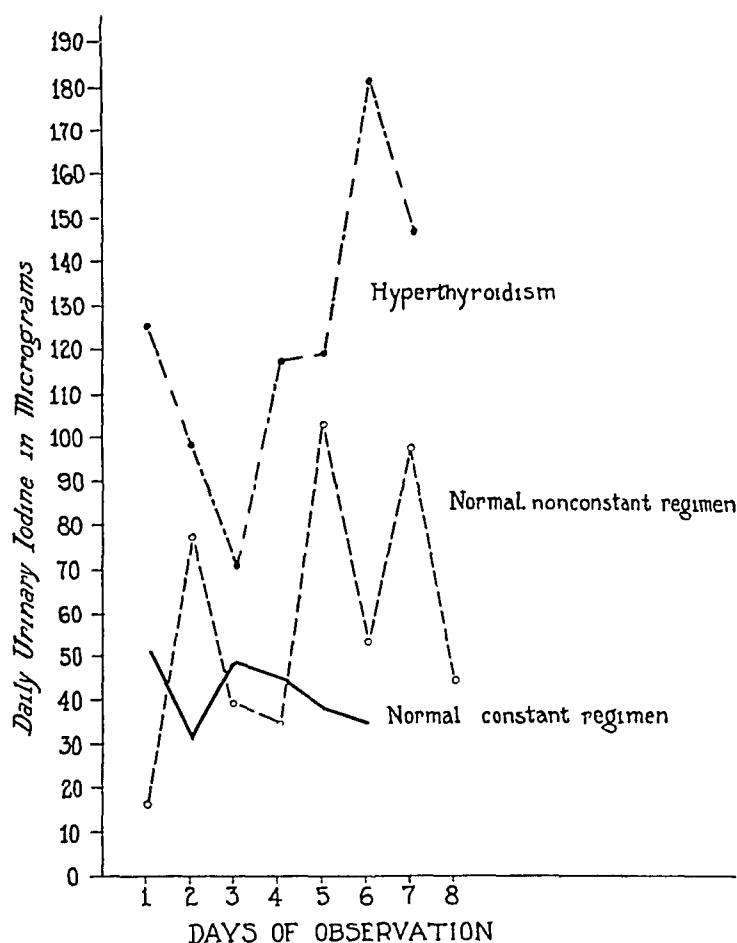


Chart showing a comparison of the urinary excretion of iodine in a patient with hyperthyroidism (L A, table 1, patient 23), in a normal patient¹ (patient C S) on a nonconstant regimen and in a normal patient^{8b} (patient R B) on a constant regimen.

times greater than the normal grand average¹ for persons in the same region. This increase in the urinary excretion of iodine in patients with hyperthyroidism was not necessarily accompanied with an increased

8 Puppel, I D., and Curtis, G M. (a) Calcium and Iodine Metabolism in Thyroid Disease, *Arch Int Med* **58** 957 (Dec.) 1936, (b) Unpublished data.

urinary volume. In the majority of patients it was accompanied with a greater urinary concentration of iodine (tables 1 to 4) than normal.¹

The grand average daily urinary loss of iodine in toxic nodular goiter was greater than that in exophthalmic goiter. The cause for this remains obscure.

Data (table 3) concerning the urinary excretion of iodine in mixed goiter and carcinoma of the thyroid gland with hyperthyroidism, in induced hyperthyroidism and in pseudorecurrent hyperthyroidism are presented. These findings are in harmony with those for exophthalmic goiter and toxic nodular goiter, however, there are too few cases from which to draw extensive conclusions.

These data (tables 1 to 4 and chart) show that the variability of the daily urinary excretion of iodine in hyperthyroidism was much

TABLE 4—*Summary of the Urinary Loss of Iodine in Various Types of Hyperthyroidism*

Type of Goiter	Number of Patients	Total Days of Investigation	Average 24 Hour Urinary Volume, Cc	Average Urinary Concentration of Iodine, Micrograms per 100 Cc	Limits of Daily Urinary Excretion of Iodine, Micrograms		Average 24 Hour Urinary Excretion of Iodine, Micrograms
					Low	High	
1 Exophthalmic	24	199	1,440	12.3	29	730	147
2 Nodular	9	48	1,215	20.1	31	954	214
3 Unusual forms							
Mixed	2	9	1,205	32.6	157	628	388
Carcinoma	1	13	3,540	10.2	103	832	362
Induced hyperthyroidism	1	3	1,635	41.2	302	600	467
Pseudorecurrent hyperthyroidism*	3	26	1,595	9.0	13	276	96

* Pseudorecurrent hyperthyroidism refers to recurrent hyperthyroidism following insufficient surgical removal of goitrous tissue or subsequent to removal of a single lobe.

greater than normal.¹ It ranged from 13 to 954 micrograms daily, with averages of from 30 to 593 micrograms. One hundred and ten (37 per cent) of the two hundred and ninety-eight daily determinations of the urinary iodine were normal. There was great variation (tables 1 to 4) in daily urinary excretion of iodine not only for different patients with hyperthyroidism but for the same patient. The variations ranged from the finding of all normal values for one patient (table 1, patient 13) over a period of fifteen days to the finding of all increased values in another patient (table 1, patient 24) over a period of nineteen days. Certain patients showed fluctuations from low normal to greatly increased values during successive days. These variations in the urinary excretion of iodine for the same patient and for different patients with hyperthyroidism correspond to the variations which may occur in any one of the other clinical and laboratory features of this disease.

The basal metabolic rate (tables 1 to 3) was variable. The urinary iodine content did not necessarily vary with the basal metabolic rate or with the value for blood iodine, either in the same patient or in different patients with hyperthyroidism. In 75 per cent of the forty patients the basal metabolic rate remained within the normal range. However, there was an increased blood iodine content or an increased urinary excretion of iodine or both. Twelve and one-half per cent of the forty patients showed a normal blood iodine value, but the basal metabolic rate or the urinary excretion of iodine or both were increased. In 25 per cent of the patients the average daily urinary excretion of iodine remained within normal limits. These patients showed an elevated basal metabolic rate or an increased blood iodine value or both. Gross and microscopic examination of the surgically removed goitrous tissue of the twenty-four patients with exophthalmic goiter confirmed the preoperative diagnosis of exophthalmic goiter.

Increased urinary excretion of iodine is also sometimes observed in conditions other than clinical hyperthyroidism. It may be noted in lymphatic and myelogenous leukemias,⁹ in essential hypertension, hypertensive heart disease or in certain cases in congestive heart failure,⁹ during certain phases of the menstrual cycle¹⁰ or certain stages of pregnancy,¹¹ transiently subsequent to thyroid¹² or extrathyroid operations,¹³ and during or immediately after the administration of thyroid or iodine medication¹ in any form. These conditions may be diagnostically eliminated by adequate clinical and laboratory examination of the patient.

Determinations of the blood and urinary iodine are at present of the greatest importance in recognizing cases of borderline or incipient hyperthyroidism in which there is a normal basal metabolic rate but an increased rate of iodine metabolism. They are of differential diagnostic importance in cases of neurocirculatory asthenia in which the clinical features simulate borderline hyperthyroidism but in which there is a normal iodine metabolism.^{8b}

In exophthalmic goiter there occurs an increased mobilization and elimination of the body iodine, so that the patient may be in negative

9 Curtis, G. M., and Barron, L. E. The Urinary Loss of Iodine Following Total Thyroidectomy, *Surgery* **1** 92, 1937.

10 Cole, V. V., and Curtis, G. M. Cyclic Variations in Urinary Excretion of Iodine in Women, *Proc. Soc. Exper. Biol. & Med.* **31** 29, 1933.

11 Enright, L., Cole, V. V., and Hitchcock, F. A. Basal Metabolism and Iodine Excretion During Pregnancy, *Am. J. Physiol.* **113** 221, 1935. Curtis and Barron.⁹

12 Curtis, G. M., and Phillips, F. J. The Loss of Iodine in the Urine Following Thyroidectomy in Man, *J. Clin. Investigation* **13** 777, 1934.

13 Curtis, G. M., James, A. G., and Matthews, N. L. The Postoperative Loss of Iodine in the Urine, to be published.

iodine balance ¹⁴ during certain stages of the disease even in the presence of a normally adequate intake of iodine. At present it is not certain that the incipient thyroid hyperplasia precedes or follows the onset of this process of increased utilization, mobilization and excretion of iodine. However, it is possible that the thyroid hyperplasia in hyperthyroidism is secondary to the increased loss of body iodine and is compensatory in an attempt to meet a continued bodily demand for utilizable iodine after the store of utilizable iodine has been depleted.

Increased urinary excretion of iodine by patients with hyperthyroidism (table 4) is an indication of this state of increased loss of body iodine. However, there may be an increased excretion of iodine through other channels, such as the gastro-intestinal tract ¹⁵ and the skin, ^{2b} with a normal renal excretion of iodine.

The percentage of increase in the fecal excretion of iodine in hyperthyroidism is often greater ^{14a} than that of the increased urinary excretion of iodine. Consequently, a normal urinary excretion of iodine in hyperthyroidism does not necessarily indicate that there is not a pathologically increased loss of iodine from the body. A normal urinary excretion of iodine in hyperthyroidism may be accompanied with an increased output of iodine through other channels ¹⁶ or may be a result of renal insufficiency with retention of iodine ¹⁷ or possibly a result of depletion of stored utilizable iodine.

As evidence of at least partial depletion of the depots of utilizable iodine of the body in hyperthyroidism is the decreased iodine content of the thyroid ¹⁸ in noniodized patients. Another point of evidence is the increased excretion of iodine over normal with a similar intake of iodine ¹⁹. A third point of evidence of a state of partial depletion in certain patients with hyperthyroidism is increased retention of iodine ^{8b} which occurs immediately subsequent to the administration of iodine, for instance, in iodized milk or potassium iodide. The latter evidence is also revealed in the resulting iodine-induced colloid involution, with an

14 (a) Cole, V. V., and Curtis, G. M. Human Iodine Balance, *J. Nutrition* **10** 493, 1935. (b) Puppel and Curtis ⁸.

15 Puppel and Curtis ^{8a}. Cole and Curtis ^{14a}.

16 Scheffer ^{2b}. Puppel and Curtis ^{8a}. Cole and Curtis ^{14a}.

17 Liek, E. Ist die Jodmangeltheorie des Kropfes richtig? *München med. Wchnschr.* **74** 1786 (Oct 21) 1927. Itô, Hidekazu. Ueber den Einfluss der Nierenschädigungen auf die Jodausscheidung der Nieren, *Folia pharmacol. japon. (Brev.)* **22** 49, 1936.

18 (a) Baumann, E. Ueber das normale Vorkommen von Jod im Tierkörper, *Ztschr. f. physiol. Chem.* **21** 319 and 481, 1895, **22** 1, 1896. (b) Riggs, L. W., and Beebe, S. P. The Iodine Content of Human Thyroid Glands, *J. Biol. Chem.* **6** 41, 1909. (c) Holst, J., Lunde, G., Closs, K., and Pedersen, O. Ueber den inneren Jodstoffwechsel bei primären Thyreotoxikosen (Primär-Basedow), *Klin. Wchnschr.* **7** 2287 (Nov 25) 1928.

19 Cole and Curtis ^{14a}. Scheffer ^{2b}.

increased content of iodine in the thyroid gland in exophthalmic goiter,^{18c} and by the accompanying smaller excretion of iodine as compared with the normal^{8b}

If the negative iodine balance of hyperthyroidism continues over a sufficient time, it is readily appreciated that a state of depletion of the available stores of iodine in the body may occur. The intensity of the hyperthyroidism should then change unless a sufficient amount of iodine is supplied to maintain the increased blood iodine content and the increased loss of body iodine. This state of depletion of the store of utilizable iodine of the body in the absence of a sufficient intake of iodine may actually occur and may explain at least some of the remissions of exophthalmic goiter. Further investigation of these particular problems concerning the nature of the urinary iodine and the iodine balance in hyperthyroidism should prove of the greatest importance.

SUMMARY

There is an increased urinary excretion of iodine in certain cases and phases of hyperthyroidism. The grand average value for urinary iodine in forty patients investigated over a period of two hundred and ninety-eight days was 184 micrograms per day, which is between three and four times greater than the normal grand average (51 micrograms) for persons living in central Ohio.

The grand average daily urinary excretion of iodine in toxic nodular goiter was greater than that in exophthalmic goiter. The cause for this is not clear.

The variability of the daily urinary excretion of iodine in hyperthyroidism is much greater than that of the normal urinary excretion of iodine. It ranged from 13 to 954 micrograms daily, with averages ranging from 30 to 593 micrograms. The many variations in the urinary excretion of iodine in the same patient and in different patients with hyperthyroidism correspond to the many variations which may occur in any of the other clinical and laboratory features of this disease.

An increased urinary excretion of iodine is sometimes observed also in conditions other than clinical hyperthyroidism.

Determinations of the blood and urinary iodine are at present of the greatest differential diagnostic importance in certain cases of neuro-circulatory asthenia in which the clinical features simulate borderline hyperthyroidism.

Increased urinary excretion of iodine by patients with hyperthyroidism is an indication of a state of increased loss of body iodine. However, a normal urinary excretion of iodine in hyperthyroidism does not necessarily indicate that there is not a pathologic increased loss of the body iodine. A normal urinary excretion of iodine in hyperthyroidism may

be accompanied with an increased output of iodine through other channels, or it may be a result of renal insufficiency with retention of iodine, or, possibly, a result of depletion of available utilizable iodine

Evidences of at least partial depletion of the stores of utilizable iodine in patients with hyperthyroidism are present in the decreased iodine content of the thyroid gland, the negative iodine balance even with a normally adequate intake of iodine and the increased retention of iodine which occurs immediately subsequent to the administration of iodine in any form

At present it is not certain whether the incipient thyroid hyperplasia precedes or follows the onset of this process of increased mobilization, utilization and excretion of iodine. However, it is possible that the thyroid hyperplasia in hyperthyroidism is secondary to the increased loss of body iodine and that it is compensatory in an attempt to meet a continued increased demand for utilizable iodine after the store of utilizable iodine has been consumed

A state of depletion of the store of utilizable iodine of the body in the absence of a sufficient intake of iodine may actually occur and explain at least certain of the spontaneous remissions of exophthalmic goiter. Further investigation of these particular problems concerning the nature of the urinary iodine and the iodine balance in hyperthyroidism should prove of the greatest importance

The National Research Council furnished the grant which made possible the completion of these studies. Dr Francis J Phillips and Dr Versa V Cole rendered invaluable aid during the early work. The determinations of the basal metabolic rate and the iodine analyses were made with the assistance of Norman L Matthews, J H Meyer and Ruth Bierbaum

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ELECTROLYTES OF BLOOD AND URINE OF DOGS WITH ACUTE HEPATIC INJURY PRODUCED BY ARSPHENAMINE

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Investigations of the effects of experimental hepatic injury on the chemical constituents of the blood have been of limited character. Most of the investigations have been concerned with changes in the non-protein nitrogen, urea and uric acid of the blood and alterations in carbohydrate metabolism. Minot and Cutler¹ have described increases in the guanidine base and accumulations of lactic acid in the blood in instances of damage to the parenchyma of the liver produced experimentally by carbon tetrachloride poisoning. Occasional clinical reports² have described the reduction of plasma chlorides in instances of carbon tetrachloride intoxication, while an increase in the concentration of lactic acid in the blood of patients with extensive hepatic disease has been described by several authors³.

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From the Medical Service of Dr George Baehr and the Laboratories of the Mount Sinai Hospital

1 Minot, A S, and Cutler, J T. Increase in Guanidine-Like Substance in Acute Liver Injury and Eclampsia, *Proc Soc Exper Biol & Med* **26** 607, 1929
Minot, A S. The Mechanism of the Hypoglycemia Produced by Guanidine and Carbon Tetrachloride Poisoning and Its Relief by Calcium Medication, *J Pharmacol & Exper Therap* **43** 295, 1931

2 Gautier, C, Chatron, M, and Seidmann, P. Intoxication par le tétrachlorure de carbone. Hyperazotémie élevée, effondrement de la réserve alcaline, hypochlorémie considérable, *Bull et mém Soc med d hôp de Paris* **49** 1638 (Jan 1) 1934

3 Hochrein, M, and Meier, R. Ueber den Milchsäuregehalt des Blutes, *Deutsches Arch f klin Med* **161** 59, 1928. Jervell, O. Investigations of the Concentration of Lactic Acid in Blood and Urine Under Physiologic and Pathologic Conditions, *Acta med Scandinav*, supp 24, 1928, p 1. Schumacher, H. Das Verhalten der Blutmilchsäure bei Leberkranken, *Klin Wchnschr* **7** 1733 (Sept 9) 1928

In a previous paper one of us (L J S⁴) reported the existence of changes in the electrolytes of the blood following the production of extensive hepatic damage with arsphenamine

In the present study these changes were further investigated. Determinations were made of the nonprotein nitrogen, urea, sugar, carbon dioxide, sodium, chloride, potassium, calcium, phosphorus, magnesium, total protein and lactic acid contents of the blood, as well as complete hematologic studies in several instances. In two dogs careful studies of the urine were conducted which included quantitative determinations of the total protein, chloride, inorganic phosphate and lactic acid contents

PROCEDURE

Hepatic damage was produced in dogs by intravenous injection of arsphenamine. The animals were kept on a diet of raw shin meat to which 2 Gm of salt was added daily for at least two weeks before the experiment was started. Just before the injection of arsphenamine, blood from the femoral artery was collected anaerobically for the determination of the various electrolytes

All determinations on the blood were made with serum. Sodium was studied by the method of Butler and Tuthill,⁵ potassium, by the colorimetric method of Shohl and Bennett,⁶ calcium and magnesium, by the method of Kramer and Tisdall,⁷ carbon dioxide, by that of Van Slyke and Neill,⁸ inorganic phosphate, by that of Fiske and Subbarow,⁹ chloride, by that of Van Slyke,¹⁰ lactic acid, by that of Friedemann and his associates,¹¹ urea, by decomposition with urease and direct nesslerization, ghatti gum being used as a stabilizing colloid (Folin¹²), and nonprotein nitrogen, by direct nesslerization (Wong¹³). The total protein content was determined by the refractometric method

4 Soffer, L J. Blood Electrolyte Studies in Experimental Acute Liver Injury Produced by Arsphenamine in Dogs, *Proc Soc Exper Biol & Med* **35** 160, 1936

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12 Folin, O. Supplementary Note on New Ferricyanide Method for Blood Sugar, *J Biol Chem* **81** 231, 1929

13 Wong, S Y. Use of Persulfate in Estimation of Nitrogen by Folin's Direct Nesslerization Method, *J Biol Chem* **55** 431, 1923

The methods employed for the determination of the various urinary constituents were as follows. Total protein was determined by the colorimetric method of Wu and Ling,¹⁴ chloride, by the modified Volhard-Harvey titration method,¹⁵ lactic acid, by that of Friedemann and his associates,¹¹ and inorganic phosphate, by that of Fiske and Subbarow.⁹

From 40 to 80 mg per kilogram of body weight of freshly prepared arspenamine was injected intravenously. This was usually followed in about one-half hour by vomiting, which lasted a few minutes and then subsided entirely. Five of eleven animals required subsequent injections of arspenamine for the production of icterus. Death usually occurred from twenty to twenty-four hours after the last injection of arspenamine. Samples of arterial blood were again collected for study of the electrolytes when the animal appeared definitely icteric. From six to eight hours after the appearance of jaundice the dogs became comatose and died. At no time were convulsive seizures manifested. In three instances (dogs 12, 21 and 24) there was no visible jaundice. The bilirubin content of the blood, however, was somewhat elevated, and bile was excreted in the urine. At autopsy the liver showed extensive destruction in all three instances, although the destruction was not as pronounced as in the severely jaundiced animals.

Immediately after the death of each animal autopsy was performed, and sections of the liver, kidneys and intestines were removed for microscopic study. Two of the eleven dogs presented considerable congestion of the small intestine and rectum. The kidneys appeared grossly normal in all instances. The liver felt firm but had a distinctly mottled appearance. The lobules were well outlined and were surrounded by punctate hemorrhages. The remaining organs appeared entirely normal. Microscopically the liver showed the most pronounced changes. In dog 1 there was extensive central necrosis, well over three fourths of the individual lobules being destroyed. There were some well preserved cells around the periportal spaces, but even here some necrosis was present. In many areas the necrosis extended to the portal vein. The cellular structure of the lobule was entirely destroyed. The kidneys of this animal showed much less marked changes. Many of the glomerular capsules showed the presence of a coagulated fluid. There was no actual damage, however, to the glomeruli. There was occasional necrosis of some of the cells of the tubular epithelium. The nuclei of many had disappeared. The tubular epithelium in places was swollen, granular and vacuolated. The remaining dogs showed similar microscopic changes but to varying degrees. In all instances the most pronounced changes occurred in the parenchymal cells of the liver.

RESULTS

Of the eleven dogs thus studied, nine died and two survived. Jaundice developed in the animals that survived, and the animals appeared to be as ill clinically as were those that failed to recover. However, the electrolyte pattern of the blood of these animals at the height of the illness differed from that of the other experimental animals. The details of these experiments will be described subsequently.

In eight of the eleven dogs icterus developed. The bilirubin content of the blood varied from 2 to 16 mg per hundred cubic centimeters,

14 Wu, H., and Ling, S. M. Colorimetric Determination of Proteins in Plasma, Cerebrospinal Fluid and Urine, *Chinese J Physiol* **1**:161, 1927.

15 Harvey, S. C. The Quantitative Determination of the Chlorids of the Urine, *Arch Int Med* **6**:12 (July) 1910.

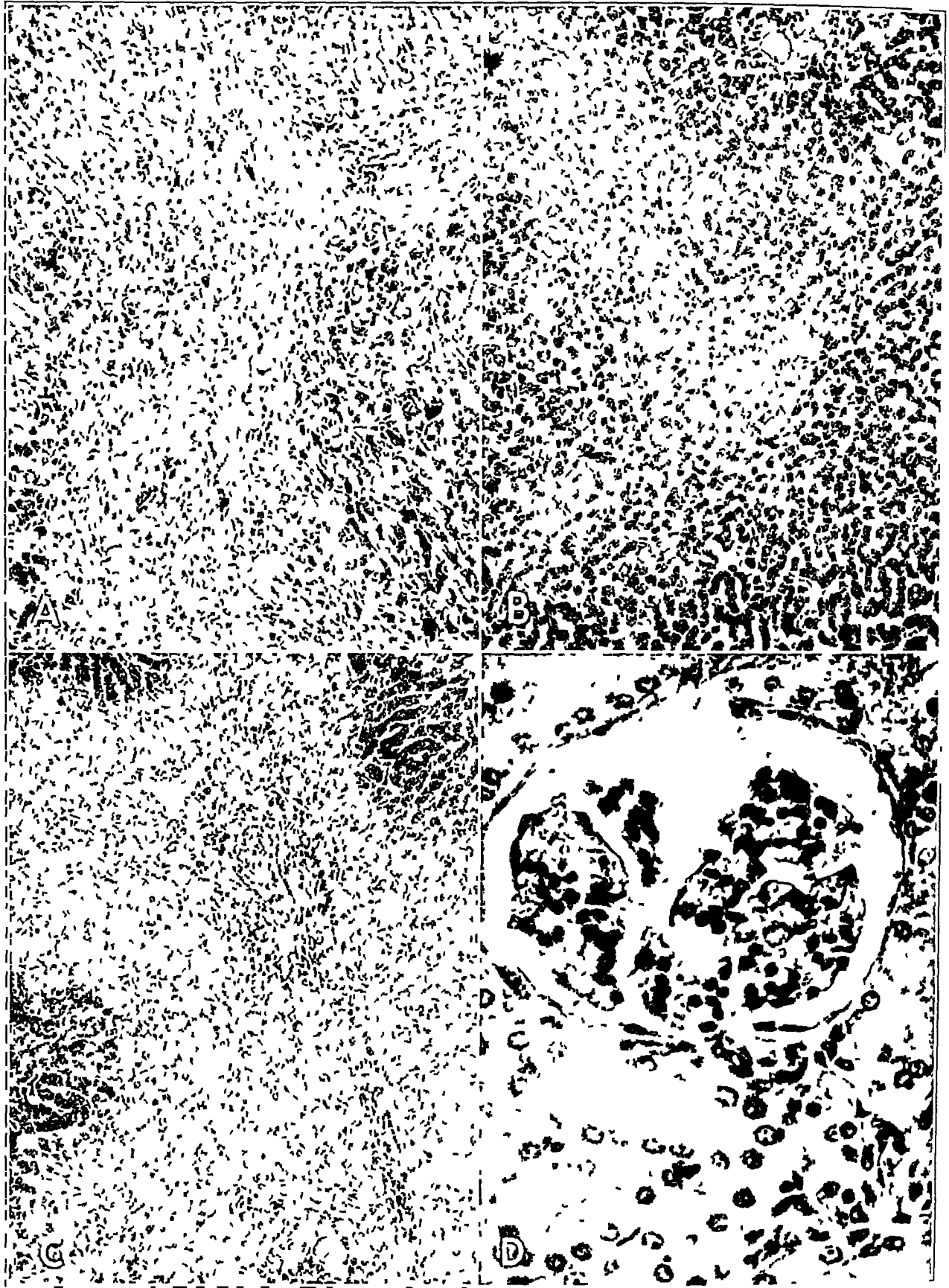


Fig 1—*A*, a section from the liver of dog 8, showing severe central destruction of the parenchyma, medium power *B*, a section from the liver of dog 12, showing mild central parenchymal destruction and congestion, medium power *C*, a section from the liver of dog 14, showing severe central parenchymal necrosis, medium power *D*, a section from the kidney of dog 1, high power. Note the tubular degeneration and exudate in Bowman's capsule

TABLE 1—*Protocols of Experiments*

Dog No	Van den Bergh Test		Icterus Index, Units	Volume of Packed Erythrocytes, Cc per 100 Cc		Volume of Packed Leucocytes, Cc per 100 Cc		Plasma Volume, Cc per 100 Cc	Date	Time		Arsphen amine, Mg per Kg of Body Weight	Intravenous Injection, Cc	Comment
	Qualitative	Quantitative		Cc per 100 Cc	Cc per 100 Cc	Cc per 100 Cc	Cc per 100 Cc							
1	Negative	0.5	6	48.5	1.0	50.5	11/26	2 30 p m	11/26	2 30 p m	60	76.0	Control	
	Delayed, biphasic	2.5	20	65.0	0.5	34.5	11/27	12 10 p m	11/27	12 10 p m			Dog died	
4	Negative	0.5	6	42.0	1.5	56.5	12/ 7	10 30 a m	12/ 7	10 30 a m	53	78.0	Control	
	Negative						12/13	2 45 p m	12/13	2 45 p m	60	88.0		
							12/18	8 00 p m	12/18	8 00 p m	70	101.5		
	Delayed, biphasic	3.6	56	51.0	0.9	48.1	12/20	8 00 a m	12/20	8 00 a m			Dog died	
8	Negative	0.5	6				7/ 8/35	10 00 a m	7/ 8/35	10 00 a m	60	56.0	Control	
	Direct	10.0	100+				7/10	10 00 a m	7/10	10 00 a m	70	66.0		
							7/11	3 30 p m	7/11	3 30 p m	80	75.0	Dog died	
							7/12	8 00 p m	7/12	8 00 p m				
10	Negative	0.5	4	33.3	1.5	65.2	7/19/35	10 00 a m	7/19/35	10 00 a m	50	61.0	Control	
	Prompt, biphasic	3.7	100	42.1	1.5	56.4	7/20/35	10 30 a m	7/20/35	10 30 a m	50	61.0	Dog died	
							7/22/35	4 00 p m	7/22/35	4 00 p m				
12	Negative	0.5	6	33.1	0.8	66.1	7/24/35	10 00 a m	7/24/35	10 00 a m	40	38.0	Control	
	Very faint, delayed, biphasic	0.5	7	41.6	2.0	56.4	7/25/35	10 00 a m	7/25/35	10 00 a m	50	47.0	Dog died	
							7/26/35	8 30 a m	7/26/35	8 30 a m				
14	Negative	0.5	5	36.4	1.5	62.1	7/29/35	10 00 a m	7/29/35	10 00 a m	40	45.0	Control	
	Direct	5.7	60	41.0	1.8	57.2	7/30/35	11 00 a m	7/30/35	11 00 a m				
	Direct	16.0	100	46.2	1.4	52.4	7/31/35	10 15 a m	7/31/35	10 15 a m			Dog died	
19	Negative	0.5	5	33.6	0.9	65.5	6/ 3/36	10 00 a m	6/ 3/36	10 00 a m	60	54.0	Control	
	Direct	2.5	30	38.1	0.6	61.3	6/ 8/36	10 00 a m	6/ 8/36	10 00 a m	80	69.0		
	Direct	5.6	90	40.0	0.6	59.4	6/10/36	11 00 a m	6/10/36	11 00 a m			Dog died	
							6/10/36	9 30 a m	6/10/36	9 30 a m				
21	Negative	0.5		38.5	1.5	60.0	9/29/36	11 30 a m	9/29/36	11 30 a m	65	65.0	Control	
	Indirect	1.0					10/31/36	2 30 p m	10/31/36	2 30 p m			Dog died	
24	Negative	0.5		32.5	2.0	65.5	10/21/36	12 00 m	10/21/36	12 00 m	70	56.0	Control	
	Indirect	0.8					10/23/36	10 00 a m	10/23/36	10 00 a m			Dog died	
3	Negative	0.5		40.0	1.5	58.5	12/ 7/34	10 30 a m	12/ 7/34	10 30 a m	55	75.0	Control	
	Delayed, biphasic	2.0		48.5	2.0	49.5	12/ 8/34	2 30 p m	12/ 8/34	2 30 p m			Dog recovered	
18	Negative	0.5	4	42.8	1.0	56.2	5/20/36	1 30 p m	5/20/36	1 30 p m	85	85.0	Control	
	Direct	4.4	50	41.5	1.0	57.5	5/21/36	4 30 p m	5/21/36	4 30 p m			Dog recovered	

TABLE 2—Serum Electrolytes in Acute Hepatic Parenchymal Damage

Dog No	Nonprotein Nitrogen, Mg per 100 Cc	Urea, Mg per 100 Cc	Sugar, Mg per 100 Cc	Carbon Dioxide		Sodium, Milli equivalents per Liter	Chloride, Milli equivalents per Liter	Potassium, Milli equivalents per Liter	Calcium, Mg per 100 Cc	Inorganic Phosphorus, Mg per 100 Cc	Magnesium, sum, Mg per 100 Cc	Lactic Acid, Mg per 100 Cc	Total Protein, Gm per 100 Cc	Date
				Content, Milli equivalents per Liter	Content, Milli equivalents per Liter									
1	26	11	80	24.4	114.4	144.6	114.4	1.0	9.6	3.4		16.4	5.6	11/26
	81	5.3	16	12.5	107.0	145.8	107.0	13.5	9.5	12.9		85.0	5.1	11/27
4	36	18	85	29.5	107.5	145.3	107.5	4.1	11.8	6.6	1.6	19.5	5.5	12/ 7
	35		85											
8	88	41	20	19.7	100.4	138.0	100.4	11.3	11.6	18.0	1.3	80.0	5.1	12/20
	31		83	26.4	110.6	147.0	110.6		10.4	3.5		13.4	1.9	7/ 8/35
10	108		100	19.5	93.6	146.9	93.6			6.6		35.8	5.2	7/11
	30	17	70	26.7	111.4	143.3	111.4	4.9	10.0	4.1	1.8	11.7	4.8	7/19/35
12	76	56	32	17.2	101.6	138.4	101.6	5.6	9.1	15.4	2.1	47.0	4.8	7/22/35
	30	12	88	22.4	109.0	140.3	109.0	4.1	10.2	4.0	1.2	13.4	7.0	7/24/35
14	128	100	92	14.6	94.8	138.2	94.8	5.7	9.3	16.0	2.4	24.6	6.5	7/26/35
	34	18	72	27.6	104.0	143.0	104.0	5.9	10.2	3.3		10.4	6.1	7/29/35
19	40	25	90	23.4	99.4	139.0	99.4		9.8	3.8		29.1	5.6	7/30/35
	90	75	50	21.4	83.8	137.1	83.8	7.6	10.4	11.4		40.2	6.1	7/31/35
21	35	15	95	26.0	108.0	140.0	108.0					70.0	6.1	7/31/35
	70	52	85	19.6	95.0	137.2	95.0							
24	28	15	85	26.8	104.0	147.5	104.0	5.5	10.5	3.8	2.3	12.9	6.7	6/ 3/36
	56	30	90	19.0	95.0	133.9	95.0	5.6	9.9	3.8	2.0	30.7	6.2	6/ 9/36
3	128	88	75	16.2	86.0	134.0	86.0	8.3	9.7	6.9	2.8	74.3	6.2	6/10/36
	35	15	95	26.0	108.0	140.0	108.0							
21	70	52	85	19.6	95.0	137.2	95.0							
	28	15	85	24.7	105.4	140.0	105.4							
24	60	40	80	19.0	96.5	136.0	96.5							
	36	15	70	27.0	109.6	145.6	109.6	3.8	11.3	6.6	1.5	18.9	5.0	10/21/36
3	50	22	75	27.4	99.0	140.3	99.0	4.4	10.9	6.9	1.5	18.9	5.0	10/23/36
	36	15	70	27.0	109.6	145.6	109.6	3.8	11.3	6.6	1.5	18.9	5.0	12/ 7/34
18	40	19	100	19.2	103.0	142.5	103.0	7.9	10.9	3.2				12/ 8/34
	33	16	120	22.0				8.2	9.2	2.0				5/20/36
18	40	19	100	19.2	103.0	142.5	103.0	7.9	10.9	3.2				5/20/36
	33	16	120	22.0				8.2	9.2	2.0				5/21/36

while the qualitative van den Bergh reaction varied from a delayed biphasic to a direct reaction. The three animals in which icterus failed to develop showed considerable hepatic parenchymal destruction, but this destruction was less than that demonstrated in the other animals. The electrolyte pattern in these dogs showed the characteristic alterations, although again to a lesser extent than in the animals in which the liver was more extensively involved. The degree of jaundice was only roughly proportional to the extent of the hepatic damage. Thus, dogs 1, 4 and 10 showed extensive hepatic damage, although the degree of bilirubinemia was much less marked than in the other dogs. The extent of the changes in the electrolytes paralleled the degree of hepatic injury.

TABLE 3—*Studies of the Blood in Experimental Acute Hepatic Parenchymal Damage*

Dog No	Erythrocytes, Millions per Cu Mm	Hemoglobin, Gm per 100 Cc	Vol of Packed Erythrocytes, Cc per 100 Cc	Vol of Leukocytes and Platelets, Cc per 100 Cc	Plasma Volume, Cc per 100 Cc	Mean Corpuscular Volume, Cu Microns	Mean Corpuscular Hemoglobin, Micrograms	Mean Corpuscular Hemoglobin Concentration, %	Date	Comments
4	6.27	13.1	42.0	1.1	56.5	67	21	31	12/ 7/34	Control After 3 repeated doses of arsphenamine
	7.71	15.5	51.0	0.9	48.1	66	20	30	12/20/34	
10	5.13	11.0	33.3	1.5	65.2	65	21	33	7/19/35	Control 78 hr after arsphenamine
	6.77	13.6	42.1	1.5	56.4	62	20	32	7/22/35	
12	5.09	10.3	33.1	0.8	66.1	65	20	31	7/24/35	Control 46 hr after arsphenamine
	6.27	14.1	40.4	1.2	58.4	64	22	35	7/26/35	
14	5.61	12.0	36.4	1.5	62.1	65	21	33	7/29/35	Control 25 hr after arsphenamine
	6.38	14.5	41.0	1.8	57.2	64	23	35	7/30/35	
	6.84	14.6	46.2	1.4	52.4	68	21	32	7/31/35	49 hr after arsphenamine

In all instances there occurred marked hemoconcentration, as determined by hematocrit studies. The reduction of plasma volume varied from 13 to 32 per cent. As is seen in table 3, this reduction in plasma volume was associated with a proportionate increase in the number of red blood cells but with no changes in the character of these cells. The mean corpuscular volume, the mean corpuscular hemoglobin and the hemoglobin concentration remained unaltered throughout the experiments. The hemoconcentration may be explained by the diuresis and to a lesser extent by the diarrhea, which occurred several hours after the administration of arsphenamine and persisted until the time of death.

CHEMICAL STUDIES OF THE BLOOD

Nonprotein Nitrogen and Urea—Ten of the eleven experimental animals showed a definite increase in the nonprotein nitrogen and urea contents. This increase in the nitrogenous constituents of the blood bore no relationship to the extent of the hepatic damage, as is shown by a comparison of the data for several dogs. In dog 1, in which most of the liver was destroyed, the nonprotein nitrogen and urea contents did not rise to as high a level as they did in dog 12, in which there was comparatively little hepatic damage. Similarly, dog 8 showed a much higher nonprotein nitrogen content than dog 10, although the degree of hepatic damage in the latter was greater than in the former. Two factors probably operated in producing this elevation of the nitrogenous constituents of the blood—the marked dehydration and the failure of renal function.

Sugar—Three of the eleven dogs showed definite hypoglycemia, the sugar content being 16, 20 and 32 mg per hundred cubic centimeters, respectively. In the fourth dog the sugar content dropped from 90 to 50 mg. None of the animals showed actual hypoglycemic convulsions. The relationship between the hypoglycemia and the lactic acid content of the blood will be discussed subsequently.

Carbon Dioxide Content—The nine dogs that died all showed reductions in the carbon dioxide content of the blood in varying degrees. The extent of the reduction was directly related to the degree of elevation of the lactic acid content of the blood and to the extent of the hepatic damage. At no time was acidosis present in the two dogs that recovered.

Sodium—Four of the eleven dogs showed no change in the sodium content of the serum during the experiment. The remaining four showed a slight drop, varying from 4 to 7.3 milliequivalents per liter.

Chloride—All the dogs showed a considerable drop in the chloride content of the serum, varying from 7.2 to 20.2 milliequivalents per liter. There was no definite relationship, however, between the degree of the drop in the chloride content and the extent of the hepatic damage. Thus, in dogs 1, 4 and 10, in which the most extensive hepatic changes occurred, the reduction of the chloride content was generally less marked than in the other dogs.

Potassium—In two of the eight dogs for which potassium determinations were obtained a conspicuous increase in this electrolyte occurred, while in the remaining six animals no appreciable change was evident. In both animals the extent of the hepatic damage was most marked, and the increase in the potassium content of the serum of these dogs (1 and 4) was probably an expression of the extensive cellular destruction of the hepatic parenchyma.

Calcium—No change in the calcium content of the serum occurred in any of the experiments, this figure remaining remarkably constant

Phosphorus—There occurred a considerable increase in the inorganic phosphorus content of the serum of all the nine dogs that died. This increase varied from one and one-half to almost four times the original control value. The increase in phosphorus was roughly proportional to the degree of elevation of nonprotein nitrogen and urea, and these increases in phosphorus failed to take place when no appreciable increase in the nitrogenous elements occurred. Thus, in dog 14 twenty-four hours after the administration of arspenamine no increase either in the nonprotein nitrogen or in the phosphorus content of the blood occurred, although already there was a considerable elevation in the lactic acid content. Similarly, in the dogs that survived, only a slight increase in the nonprotein nitrogen and urea contents occurred, with no increase in the value for phosphorus. As has been pointed out,¹⁶ this increase in inorganic phosphorus is probably an expression of the failure of renal function.

Magnesium—For the five animals on which studies of the magnesium content were made, the original control figures were doubled or trebled in three of the four animals that subsequently died, while no elevation of magnesium occurred in the animal that survived. These changes in the magnesium also are probably an expression of renal failure.

Total Protein—No change in the total protein content was noted in any of the experiments. With the development of considerable hemoconcentration one would expect that a proportionate increase in the protein content would follow. However, that this did not occur is explained by the fact that considerable quantities of protein were lost in the urine.

Lactic Acid—All of the nine animals that died showed a marked elevation in the lactic acid content of the blood. The increase varied from two to seven times the original control value.

STUDIES OF THE URINE

In two instances (dogs 21 and 24) careful urinary studies were conducted. The animals were placed in metabolism cages and kept there throughout the duration of the experiment.

The specimens of urine were collected under toluene and kept in the refrigerator until aliquots were removed for analysis. The intake of fluid and the output of urine were measured during twenty-four hour periods. The results are recorded in table 4.

16 Marriott, W. M., and Howland, J. Phosphate Retention as a Factor in the Production of Acidosis in Nephritis, *Arch Int Med* **18** 708 (Nov) 1916.

After the administration of arsphenamine there occurred an increase in the output of urine. Only terminally was there actual urinary suppression. With the diuresis there also occurred an increase in the excretion of the lactic acid, while the urinary excretion of chloride and inorganic phosphate was markedly diminished. The latter was due to failure of renal function and probably explains the high level of this electrolyte in the blood. This is further evidenced by the fact that the phosphorus content of the blood increased toward the terminal phase of the experiment, when the nonprotein nitrogen and urea contents were considerably elevated.

TABLE 4—*Study of the Urine in Experimental Acute Hepatic Parenchymal Damage*

Dog No	Date (24 Hr Period)	Fluid Intake, Cc	Urinary Output, Cc	Total Protein, Mg per 100 Cc	Lactic Acid, Mg per 100 Cc	Chloride, Milli equivalents per Liter	Inorganic Phosphate, Mg per 100 Cc	Comment
21	10/25 to 10/26	211	311	0	22.0	186.0	73.0	Control 65 mg. of arsphenamine per kilogram injected intravenously
	10/29 to 10/30	543	372	160	42.0	26.5	70.2	
	10/30 to 11/1	360	500	420	50.5	14.5	40.0	
24	10/20 to 10/21	200	140	0	15.0	154.0	127.0	Control 70 mg. of arsphenamine per kilogram injected intravenously
	10/21 to 10/22	800	460	0	48.8	29.5	78.0	
	10/22 to 10/23	330	500	300	60.6	21.4	40.0	

COMMENT

Certain aspects of this investigation must be borne in mind. These studies represent acute experiments in which hepatic damage was produced suddenly and extensively and in which death occurred within twenty-four to seventy-two hours after the administration of the drug Arsphenamine, which was used to produce the hepatic parenchymal injury, also produced definite, although slight, renal damage. The electrolyte changes in the blood incidental to the renal damage may, however, be distinguished from changes in the chemistry of the blood which are due to failure of hepatic function.

The most striking changes in the experiments are the hemoconcentration and alterations in the chemistry of the blood. In these alterations the changes of major interest are the acidosis, the hypochloremia, the accumulation of lactic acid in the blood and, incidental

to the latter, the hypoglycemia. The acidosis is due essentially to the increase in lactic acid. The increase in lactic acid is an expression of the failure of the hepatic parenchyma to convert the lactic acid into glycogen. Lactic acid is a normal product of muscular activity, and the phenomena which lead to its appearance have been elucidated by Fletcher and Hopkins,¹⁷ Meyerhof¹⁸ and Hill.¹⁹ During muscular contraction glycogen is decomposed to form lactic acid, and during the recovery phase most of the formed lactic acid is reconverted into glycogen. It must be remembered that the muscles are not the only site of glycogen \rightleftharpoons lactic acid transformation. Himwich, Koskoff and Nahum²⁰ have shown that the venous blood of almost all the organs of the body contains more lactic acid than does the arterial blood. This suggests that the conversion of glycogen into lactic acid and the reversion of the latter into the former may and do occur anywhere within the body, except in the liver and in the heart. In the liver the lactic acid is removed from the blood stream, converted into glycogen and stored as such. Cori and Cori²¹ have shown that the lactic acid content of the blood increases after the injection of epinephrine and that after the injection the hepatic glycogen is increased at the expense of the muscle glycogen. Soskin²² has shown that epinephrine exercises no effect on the blood sugar of abdominally eviscerated dogs, while Mann and Magath²³ have shown that hepatectomized dogs can succumb to hypoglycemia even when the muscles contain large amounts of glycogen. It becomes evident that muscle glycogen is not directly available for the restoration of blood sugar when the latter becomes depleted but that it must first be converted

17 Fletcher, W. M., and Hopkins, F. G. The Respiratory Process in Muscle and the Nature of Muscular Motion, *Proc Roy Soc, London*, s B **89** 444, 1917

18 Meyerhof, O. Chemical Dynamics of Life Phenomena, Philadelphia, J. B. Lippincott Company, 1924

19 Hill, A. V. The Mechanism of Muscular Contraction, *Physiol Rev* **2** 310, 1922

20 Himwich, H. E., Koskoff, Y. D., and Nahum, L. H. Changes in Lactic Acid and Glucose in the Blood on Passage Through the Organs, *Proc Soc Exper Biol & Med* **25** 347, 1928

21 Cori, C. F. The Influence of Insulin and Epinephrine on the Lactic Acid Content of Blood and Tissues, *J Biol Chem* **63** 253, 1925. Cori, C. F., and Cori, G. T. The Mechanism of Epinephrine Action. I. The Influence of Epinephrine on the Carbohydrate Metabolism of Fasting Rats, with a Note on New Formation of Carbohydrates, *ibid* **79** 309, 1928

22 Soskin, S. Muscle Glycogen as a Source of Blood Sugar, *Am J Physiol* **81** 382, 1927

23 Mann, F. C., and Magath, T. B. Studies on the Physiology of the Liver. III. The Effect of Administration of Glucose in the Condition Following Total Extirpation of the Liver, *Arch Int Med* **30** 171 (Aug) 1922

into lactic acid, which is reconverted into glycogen, mostly by the liver, and then becomes available as a source of blood sugar

In the light of this explanation the reason for the accumulation of lactic acid in the blood in our experiments becomes evident. The development of hypoglycemia in four of the experimental animals is readily explained by the inability of the liver to convert lactic acid into glycogen and hence a lack of available glycogen to be converted into dextrose when the need arises.

The increase in the lactic acid content of the blood is roughly proportional to the extent of the damage to the liver.

In dogs 3 and 18, which survived, no increase in the lactic acid content of the blood occurred, despite the fact that the animals showed icterus that was apparently indicative of some hepatic parenchymal damage. One of these animals showed some hemoconcentration and hypochloremia. The other electrolytes were entirely normal.

The relationship between the hypochloremia and the hepatic and renal damage is more complex. Hypochloremia commonly occurs in the terminal stages of nephritis. Trusler, Fisher and Richardson²⁴ have explained the low values for blood chloride in dogs poisoned with mercury bichloride as due to the severe vomiting and diarrhea which follow the administration of the poison. However, in interpreting the results of our series of experiments it must be remembered that vomiting occurred only directly after the administration of the arsphenamine, while diarrhea, although present, was at no time pronounced.

It may be that the drop in the chloride value represents an effort toward chemical adjustment in the serum. Atchley and Benedict²⁵ have shown that after ligation of the ureters of the dog there occurs a decrease in the carbonate and chloride contents of the blood which is equal to the increase in inorganic phosphate and sulfate.

SUMMARY

Studies of the electrolytes of the blood and urine are reported for dogs in which acute diffuse hepatic parenchymal damage was produced by the intravenous injection of arsphenamine.

The most outstanding changes consisted of pronounced hemoconcentration, a drop in the chloride and carbonate contents and an increase in the inorganic phosphate and lactic acid contents of the serum. In

24 Trusler, H. M., Fisher, W. S., and Richardson, C. L. Chemical Changes in the Blood in Mercuric Chloride Poisoning. Mechanism and Significance of Hypochloremia, *Arch. Int. Med.* **41**: 234 (Feb.) 1928.

25 Atchley, D. W., and Benedict, E. M. The Distribution of Electrolytes in Dogs Following Ligation of Both Ureters, *J. Biol. Chem.* **73**: 1, 1927.

three of the eleven dogs severe hypoglycemia developed. The reasons for the accumulation of lactic acid in the blood and the mechanism of the development of the hypoglycemia are described. While the latter changes are due to hepatic injury, increase in the blood phosphate probably represents a manifestation of failing renal function. The reasons for the drop in the chloride value are less clear. The vomiting was not severe enough to explain the considerable drop which occurred in this electrolyte.

A slight drop in the sodium content of the serum occurred in four of the seven animals. Two animals showed a considerable increase in serum potassium, while none of the animals showed any changes in the serum calcium.

After the administration of arsphenamine there occurred an increase in the volume of urine, with a considerable increase in the urinary excretion of lactic acid and total protein, while there was a marked reduction in the excretion of chloride and inorganic phosphate.

Progress in Internal Medicine

PERIPHERAL VASCULAR DISEASES

A REVIEW OF SOME OF THE RECENT LITERATURE AND A
CRITICAL REVIEW OF THE SURGICAL
TREATMENT

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CHICAGO

A REVIEW OF SOME OF THE RECENT LITERATURE
By DR SCUPHAM

It has become noticeable, particularly in the last year, that interest in disorders of the blood vessels of the extremities is no longer confined to special groups working in large centers of population. The great number of papers appearing on this subject from all parts of this country and of the world are evidence of the widespread interest and appreciation of the importance of a subject which only in the last few years has become generally recognized. Many of these papers are case reports or short articles on diagnosis and treatment and consist of brief summaries of generally accepted methods.

The painstaking and careful work of many years on the physiology both normal and abnormal of the blood vessels by Sir Thomas Lewis¹ has been embodied in practical form in a small volume entitled "Vascular Disorders of the Limbs." This book is a summary of the views of this author, written in his usual simple and expressive style, and covers the disorders of the blood vessels of the extremities. It has been written for students and practitioners, and the author's views are expressed briefly and concisely. No attempt will be made to review this volume or many of the papers which have appeared during the past year. Some of the more significant ones or those which seem to emphasize some important feature will be included.

¹ Lewis, Thomas. Vascular Disorders of the Limbs Described for Practitioners and Students, New York, The Macmillan Company, 1936

GLOMUS TUMORS

In a previous review² the subject of the arteriovenous anastomoses between the arterioles and the venules in the skin, particularly the work of Popoff, was reviewed. At that time no mention was made of the glomus tumor. Reports of this type of new growth have been occasional for many years. Several papers have appeared recently which again draw attention to this condition and clarify the clinical and pathologic aspects of this peculiar new growth which arises from the Suquet-Hoyer canals.

Theis³ briefly reviews the literature on this subject and reports a case of subungual neuromyo-arterial glomus tumor of the toe occurring in a patient treated for arteriosclerosis obliterans by suction and pressure therapy. The author's observations and comment are in essential agreement with those of Chiari.⁴ Pain is the outstanding symptom, and Chiari emphasizes it as being exceedingly severe, sharp and burning. It may radiate up the entire extremity, so that when the tumor is located on a finger the pain may extend into the shoulder and even into the neck. The pain is dependent on distention of the tumor mass, with blood filling the small channels and thus causing pressure on the numerous small nerve fibers which make up a large part of the matrix of the growth. Pain is intensified by heat, and in Theis' patient it became much more marked after alternating pressure and suction treatment, when the circulation was improved. Cold and pressure on the tumor may shunt the flow of blood outside through collateral channels. Pain is then relieved.

These tumors are small, seldom being more than a few millimeters in diameter. They are located on the hands and feet, a few of them being subungual. Others appear on the palms or soles and some higher on the extremities. They are bluish red when filled with blood and present many of the characteristics of a varix. Chiari states that they occur with equal frequency in males and females. The ages of the patients vary from childhood to senility. Trauma has been designated as being an important factor. The tumors seem never to be malignant, and no recurrences after excision have been reported. Chiari states that the tumors show the characteristic vessels of the normal glomus structure but are dilated and filled with blood. They are thick walled,

2 Scupham, George W., and de Takáts, Geza. *Peripheral Vascular Diseases. A Review of Some of the Recent Literature, with a Critical Review of Surgical Treatment*, Arch Int Med **58** 531 (Sept.) 1936.

3 Theis, Frank V. *Subungual Neuromyo-Arterial Glomus Tumor of the Toe*, Arch Surg **34** 1 (Jan.) 1937.

4 Chiari, H. *Zur Pathologie der peripheren Gefasse*, Wien klin Wchnschr **50** 395 (March 26) 1937.

with large cells and occasional typical smooth muscle fibers. The type of cell may vary considerably in different specimens. In some the endothelial cells predominate, and in others the matrix of the tumor is largely made up of muscle fibers or elastic fibers through which pass numerous nerve fibers. In some instances the growth resembles an endothelioma and in others a myoma.

CAPILLARIES

Roboz⁵ has attempted the use of a method for measuring capillary function which he calls the vasothermal capillary reaction. He measured the flow of blood in the capillaries of the nail bed at room temperature and after immersion of the hand in water at 50 C. Distinct types of reactions in the capillaries were noted. The typical reaction occurred in the majority of persons observed. In these the circulation time after immersion in warm water increased so much that during a ten minute period of observation the capillary blood flow could not be measured. In the atypical type of reaction the speed of the corpuscular stream through the capillaries became measureable in four minutes or less. In a few instances there was a paradoxical reaction, in which the stream of corpuscles came to a standstill after exposure to heat. Roboz found that when the capillary bed was typical morphologically, the reaction was always typical. The converse was also true. When the functional test gave an atypical reaction there was an atypical capillary pattern. This reaction is likewise dependent on the functional state of the capillary wall, particularly in regard to its tonus. In acrocyanosis the corpuscular stream was stationary at room temperature and never reached the proportions of the typical reaction. In four persons who stammered, variable circulation times were noted in different capillaries. These variations seemed to be characteristic in other types of vasoneuroses. The value of this type of observation is not yet established, but further studies may throw light on some of the minor functional disturbances of circulation in the hands and feet about which relatively little is known.

INTERMITTENT CLAUDICATION

The reason for the development of pain in muscles which are deprived of adequate blood supply has been a matter of speculation for many years. Numerous theories have been advanced, most of them to be disproved. Veal and McFetridge⁶ made an arteriographic study

⁵ Roboz, P. Beitrage zur Funktionsprufung der Capillaren, Klin Wchn-schr **15** 968 (July 4) 1936

⁶ Veal, J. Ross, and McFetridge, E. M. Vascular Changes in Intermittent Claudication, with a Note on the Value of Arteriography in This Symptom Complex, Am J M Sc **192** 113, 1936

of a group of patients with intermittent claudication and found no evidence of vascular change either after an attack, when pain was at its height, or after treatment of the condition, when the subjective state of the patient was much improved. These authors feel that arterial spasm plays no part in the condition.

The views of Lewis and his associates are generally accepted as the best explanation for the phenomenon.

Elliott and Evans⁷ have attempted to confirm the view that the substance released by muscle activity which is responsible for the production of pain by its effect on nerve endings in the muscles is probably the lactate ion or a substance the metabolism of which is closely related to that of lactic acid. They believe that this hypothesis explains the experimental results which they obtained and that the production and disposal of lactic acid and the "pain substance" are subject to similar metabolic laws. Experiments were conducted on healthy young adults with the blood supply to the arm occluded by pressure of 200 mm of mercury. They found that the presence of lactic acid in the blood, whether produced by exercise, epinephrine or sodium lactate, was regularly accompanied with an earlier appearance of ischemic pain in the muscles of the forearm than in those of the controls. This effect usually outlasted the rise in the lactic acid content of the blood, but in no instance did exercise tolerance return to normal in the phase of continuing acidemia. Decreased exercise tolerance of the forearm often occurred without a rise in the lactic acid content of the blood. The authors explain that the lactic acid content of muscles about the nerve endings may remain elevated while the value for the blood returns to normal. The typical course of events in most of their experiments was a rapid drop in exercise tolerance during the first fifteen to thirty minutes of induced acidemia. When the diffusion rate is rapid, this is followed by flattening out of the curve of exercise tolerance as diffusion from blood to tissues becomes slow. A gradual recovery by the reversal of the direction of diffusion occurs after the concentration of the blood has fallen to normal.

The authors state that some of their observations are not in strict agreement with the hypothesis that lactic acid is the sole substance responsible for ischemic muscle pain. In these experiments no rise in the lactic acid content of the blood was encountered, but the decrease in exercise tolerance was consistent and unmistakable and was comparable with that occurring from induced acidemia. These results followed exercise of the legs and the trapping of the "pain substance"

⁷ Elliott, A. H., and Evans, R. D. Ischemic Pain in Exercising Muscles, *Am Heart J* **12** 674, 1936.

in the forearm after its release from the legs. They think this may indicate that another substance or other substances may be capable of producing ischemic pain.

DIAGNOSTIC METHODS

Methods for the diagnosis of peripheral vascular disease have been so well established that relatively little has been added during the past year. The large number of papers reporting on these conditions are summaries of previous and now generally accepted work.

Battro and Lanari,⁸ however, suggest the use of acetylcholine by intra-arterial injection as an excellent, simple and harmless test to differentiate functional and organic disturbances. In functional disturbances the changes following the injection of acetylcholine do not differ from those noted in normal persons. In the presence of organic lesions when the main artery is occluded, the oscillographic findings remain unchanged below the site of the occlusion. The status of the collateral circulation is gaged by the degree, distribution and rapidity of appearance of the change in color which occurs after the injection of acetylcholine. This likewise furnishes information as to the site for amputation. It may be that this method for the release of vascular tone is of some importance. It is at least as difficult as the nerve block procedure and certainly no more effective. It surely carries greater possibility for unfavorable consequences.

Collens and Wilensky⁹ report two objective tests for the measurement of peripheral vascular obstruction. One of these tests measures the claudication time and the other the venous filling time. The latter test is carried out by placing the patient in a recumbent position with one foot or hand elevated as high as possible. The patient then alternately flexes and extends the digits until blanching occurs. The extremity is then lowered below the level of the bed. The veins are collapsed. The time required for the blood to show the first sign of distending the vein is noted. Normally this is in from seven to ten seconds, in patients with pathologic conditions it has been noted to extend as long as two minutes. The longer the filling time, the greater the degree of vascular obstruction.

Measurements of the temperature of the skin remain the most widely accepted measurement of the peripheral blood flow.

Arteriography—Most workers in the field of arteriography seem to have arrived at similar conclusions in regard to the value of this

8 Battro, A., and Lanari, A. Inyeccion intraarterial de acetilcolina, su valor diagnostico en las afecciones vasculares perifericas, *Rev argent de cardiol* **3** 31, 1936.

9 Collens, William S., and Wilensky, Nathan D. Two Quantitative Tests of Peripheral Vascular Obstruction, *Am J Surg* **34** 71, 1936.

method As recorded in previous reviews, the characteristic appearances of the arteriographic picture in several pathologic disorders as well as in the normal state are distinct Certain precautions in regard to interpretation are stressed by Yater¹⁰ and by Allen¹¹ This is particularly true in regard to colloidal thorium dioxide, which, when injected into the blood stream, rapidly leaves the vascular system, so that the time between the injection and the exposure of the film must be brief In some instances complete filling of the distal arteries may not have occurred and may lead to errors in diagnosis This happens particularly if the exposure has been made too quickly, or it may be due to other variations in technic Thorium dioxide is the substance which is almost universally used in this country While there still seems to be some doubt as to the possibility of latent damage from the use of a radio-active substance, up to this time no bad effects have been recorded in this country Yater,¹⁰ in his excellent paper, discusses the form of the normal arteriogram as well as that seen in patients with typical disease conditions His ideas agree with those of others previously reported He states that though there may be many variations of the normal vascular tree of the extremities, the main arteries usually conform to a standard pattern Owing to the state of the circulation and the lag in the diffusion of thorium dioxide, only a certain number of vessels are made visible at the same time This is characteristic of the normal arteriogram, in which the arteries appear to be smooth walled and to have a relatively direct course The fact that the normal arteriogram shows only the larger and more direct vessels probably explains why it is that these are the ones usually affected by degeneration They bear the brunt of the circulatory load, and this factor of stress is important in the localization of degenerative disease The smaller vessels and branches are often less severely affected and take up the function of the collateral circulation

The description that Yater gives of arteriosclerosis and thrombo-angitis obliterans is essentially the same as that recorded in previous reviews He states that arteriography shows that thrombo-angitis obliterans is a polyphasic disease, in that various stages are present in the various arteries and their branches at the same time Disease of the collateral circulation is the most extensive of all vascular diseases The author notes that arterial spasm of a severe type may occur with arterial puncture in this condition as well as in Raynaud's disease

10 Yater, Wallace M Thorotrast Arteriography of the Extremities, with Report of Illustrative and Unusual Cases, *Am Heart J* **12** 383, 1936

11 Allen, E V The Peripheral Arteries in Raynaud's Disease An Arteriographic Study of Living Subjects, *Proc Staff Meet, Mayo Clin* **12** 187 (March 24) 1937

Arteriovenous fistula and aneurysm can be well demonstrated. He emphasizes that the importance of arteriography is in selecting the best site for amputation. He agrees with others that it affords an excellent method for study of vascular disease in living subjects, but he does not regard it as a necessary diagnostic procedure except in cases in which the clinical diagnosis is difficult.

This is emphasized in the report of a case by Baker and Allen,¹² in which the diagnosis of the disease was not apparent on clinical examination. In this case the arteriogram was characteristic of thromboangitis obliterans and served to confirm the clinical diagnosis.

Allen¹¹ made a study of 22 patients with Raynaud's disease who showed all the symptoms pointing to a diagnosis of this condition. He summarizes the findings as follows: "There was an absence of filling of the radial arteries in two cases, normal filling of all arteries in four cases, absence of filling of the digital portions of more than one or two digital arteries in sixteen cases, and small caliber of some or all the digital arteries in eighteen cases." He does not consider incomplete filling of the digital portions of the digital arteries as evidence of inherent arterial disease. It seems to indicate a functional disorder. Arteriograms were also made for asthenic persons who did not have Raynaud's disease. The appearance of the arteriograms in these instances was the same as that noted in Raynaud's disease. After removal of the cervical thoracic sympathetic ganglions in Raynaud's disease arteriograms may or may not produce normal filling of digital arteries which did not fill normally before operation. The author concludes that if a local fault is responsible for Raynaud's disease, it does not appear in arteriograms to be organic.

Ratschow¹³ agrees that the importance of arteriography lies principally in the estimate it allows of the efficiency of the peripheral circulation, in regard to both the arteriogram and the venogram. He thinks that the method has made it possible to demonstrate the various factors which influence the flow of blood in the veins. The efficiency of the compensating channels in a patient with varicose veins can be determined to much better advantage than by any other method. The same applies to the collateral circulation in regard to selection of the site for amputation. The author's work has been with neo-iopax and abrodil (the sodium salt of mono-iodomethane sulfonic acid). These substances

12 Baker, T. W., and Allen, E. V. Diagnostic Value of Arteriography. Report of a Case, *Proc. Staff Meet., Mayo Clin.* **11**: 500 (Aug. 5) 1936.

13 Ratschow, M. Leistung und Bedeutung der Vasographie als Funktionsprüfung der peripheren Blutgefäße, *Fortschr. a. d. Geb. d. Röntgenstrahlen* **55**: 253, 1937.

have been shown to be satisfactory, particularly for venography. The pain produced by the intra-arterial injection of the substances is difficult to explain. It can largely be minimized by the periarterial injection of procaine hydrochloride at the site of the puncture. In arteriograms made serially he has been able to follow the contrast medium to the smallest vascular branches.

Veal and McFetridge⁶ have made an arteriographic study of intermittent claudication in 15 carefully selected patients. Syphilis and thrombo-angitis obliterans were eliminated. In 12 the cause was arteriosclerosis, and in 3 others the etiologic basis could not be determined. Thorium dioxide was the contrast medium used. The authors were able to divide the patients into three distinct groups. The first included those in whom the cause was arteriosclerosis and in whom the most outstanding change was obliteration of the large arteries. There was a diminution in the number of large muscular branches, and their distribution was uneven and clearly inadequate. In the second group of arteriosclerotic patients the large arteries were not obliterated, but their lumens were narrowed. There was also a marked diminution in the size of the muscular branches and in the number of small terminal vessels. The third group included those for whom a diagnosis could not be made. The arteriograms showed no change in the main arteries in 1 patient, narrowing of the popliteal and tibial arteries was noted in the second, and complete occlusion of the popliteal artery was noted in the third. The characteristic finding in all 3 patients was a peculiar clubbing and dilatation of the muscular branches, which terminated abruptly.

With exercise and the appearance of intermittent claudication, it was not possible to show any decrease in the size of the vessels or in the form of the arteriogram, except that the vessels in some instances appeared to be actually dilated. In 1 patient the improvement in the clinical condition which followed treatment could not be correlated with any change in the form of the arteriogram. The authors are certain that intermittent claudication could not have been due to arterial spasm, from the evidence produced by arteriography. They believe that the method is a valuable means of making a definite diagnosis in cases of pain in the extremities in which a vascular lesion may not be evident.

Veal and McCord¹⁴ emphasize the value of arteriography in the diagnosis of abnormal arteriovenous communications in the extremities. It is the only method by which the number, location, type and size of the communicating passages may be demonstrated.

14 Veal, J. Ross, and McCord, William M. Congenital Abnormal Arteriovenous Anastomoses of the Extremities, with Special Reference to Diagnosis by Arteriography and by Oxygen Saturation Test, *Arch Surg* **33** 848 (Nov.) 1936.

THROMBO-ANGIITIS OBLITERANS

The fact that the pathologic characteristic of thrombo-angitis obliterans presents the picture of an inflammatory process has led most workers to believe that this disease is actually a bacterial inflammatory condition. No absolutely conclusive proof has been brought to bear on this subject. There has been considerable difficulty in transmitting the infection to experimental animals. A case of accidental transmission of the disease from man to man has been reported by Allen and Lauderdale¹⁵. They review the literature on this subject and report the case of a surgeon 45 years of age who, while amputating the toe of a man with thrombo-angitis obliterans, accidentally suffered a wound of a finger by a spicule of bone from the patient's toe. One month later color changes, consisting of cyanosis and pallor on exposure to cold, appeared in this finger and somewhat later two other fingers of the same hand became involved. Examination six months later revealed a reduction in the cutaneous temperature and abnormal pallor of these fingers. The temperature of these digits after ingestion of ethyl alcohol remained below that of the other hand. From the clinical findings it seems that the diagnosis in this case was correct and that it is highly probable that the disease resulted from transmission of the infection rather than being a mere coincidence.

Friedlander, Laskey and Silbert¹⁶ have continued their work on the relation of blood volume to endocrine function. Part of this material was reviewed last year. In an additional paper they discuss the effect of estrogenic substance on blood volume. Study revealed a consistent rise in blood volume to normal levels after treatment with estrogenic substance in all groups of patients in whom the initial blood volume was low. The reduction in blood volume which follows bilateral oophorectomy was compensated for in 5 patients who were given estrogenic substance. In 7 men with thrombo-angitis obliterans the same result was obtained, while in 2 normal women who showed a normal initial blood volume and in 4 normal cats no changes were produced. Male cats which had been subjected to thyroidectomy likewise showed a reduction in blood volume, which could be restored to normal by administration of the hormone. While no absolute conclusion can be drawn from this work, it may be of some importance in explaining the reason for the relative infrequency of the disease in females.

15 Allen, E. V., and Lauderdale, T. L. Accidental Transmission of Thrombo-Angitis Obliterans from Man to Man, *Proc. Staff Meet., Mayo Clin.* **11** 641 (Oct. 7) 1936.

16 Friedlander, Mae, Laskey, Norman, and Silbert, Samuel. Effect of Estrogenic Substance on Blood Volume, *Endocrinology* **20** 329, 1936.

Two cases of thrombo-angitis obliterans in women have been reported. One of these is reported by Herrell and Allen,¹⁷ who comment again on the rarity of the disease in women. They conclude that there is considerable question of the diagnosis in several of the cases that have been reported. Their patient was a Scandinavian woman aged 41, who presented characteristic vasomotor disturbances and typical intermittent claudication. Occlusion of the larger arteries of the leg and superficial phlebitis were observed. The disease was progressive and arteriosclerosis could not be demonstrated. The patient used tobacco excessively. The authors believe the criteria for the diagnosis of the disease has been fulfilled. Van Dellen and Wright¹⁸ report the case of a Russian Jewess of 46 who likewise presented symptoms and findings which could be considered characteristic of the disease. It is to be noted that in both cases, as in most of the others reported in women, the disease was relatively mild and seemed to respond fairly well to therapy.

Several interesting cases of the disease in Negroes have been reported in the last year. Parson¹⁹ describes a case in a man who was five-eighths white. This seems to be an authentic case, although the patient had syphilis and pathologic confirmation is lacking. Smith²⁰ describes another case in a Negro, and Yater²¹ reports 5 additional cases which seem to fulfil the requirements for the diagnosis of this disease. The patients were all full-blooded Negroes, as nearly as could be determined. Pathologic and arteriographic examinations confirmed the diagnosis. All the men had syphilis, but Yater states that the incidence of the disease in Negroes is so high that the association of the two conditions may have been purely accidental. Pathologically the lesions were not suggestive of syphilis, nor is syphilis of the medium-sized arteries at all common. Yet Yater does not exclude the possibility that there may be some causal relationship.

Further studies on the effect of tobacco on the cardiovascular system have been made by Maddock, Malcolm and Coller.²² They found no relationship between cutaneous sensitivity to tobacco and the fall in temperature of the digits and the rise in blood pressure with smoking.

17 Herrell, Wallace E., and Allen, Edgar V. Thrombo-Angitis Obliterans in Women. Report of a Case, *Am Heart J* **12** 105, 1936.

18 Van Dellen, T. R., and Wright, I. S. Thrombo-Angitis Obliterans in Women. Report of a Case, *Am Heart J* **13** 373, 1937.

19 Parson, G. W. Case of Thrombo-Angitis Obliterans in Negroid, *Texas State J Med* **32** 546, 1936.

20 Smith, C. A. Thrombo-Angitis Obliterans. Report of a Case in Negro, *Texas State J Med* **32** 462, 1936.

21 Yater, Wallace M. Thrombo-Angitis Obliterans in Negroes, *Am Heart J* **13** 511, 1937.

22 Maddock, Walter G., Malcolm, Russell L., and Coller, Frederick A. Thrombo-Angitis Obliterans and Tobacco, *Am Heart J* **12** 46, 1936.

The effects of cigaret smoking were observed on both men and women, and the results were essentially the same, the reductions in the temperature of the digits with increases in blood pressure and in pulse rate were similar in the two sexes. Similar experiments carried on with Jews showed a greater drop in the temperature of the fingers than occurred in gentiles. The authors think that this may account for the greater incidence of thrombo-angitis obliterans among Jews than among other elements of the population. No explanation of this fact is offered. The authors feel that cigaret smoking definitely reduces the blood supply to the extremities and for this reason is an important predisposing factor in the development of thrombo-angitis obliterans.

Ratschow²³ investigated the effect of exposure to cold and wet as an etiologic factor in peripheral vascular diseases. In thrombo-angitis obliterans as well as in other circulatory disorders he found that occupation was not an important factor. Study of the disease among men and women engaged in the fishing industry, in which exposure to cold and water is excessive, showed that there has not been a single case in four years.

All the patients with thrombo-angitis obliterans were divided into five groups according to occupation: (1) sedentary occupations without exposure (23 men), (2) manual labor without exposure (38 men), (3) light labor with occasional exposure to cold (20 men), (4) hard labor with occasional exposure (17 men) and (5) hard labor with constant exposure to cold and wetness (11 men). He points out that while exposure plays no part as an etiologic factor, there is a constitutional vascular defect which is the probable underlying cause.

In discussing thrombo-angitis obliterans Yanovsky²⁴ says he considers that the disease should be called *neuro-angitis obliterans*, because of the involvement of the sympathetic nerves and blood vessels in the pathologic process. He emphasizes the importance of the involvement of the sympathetic nerves, particularly the sympathetic fibers in the adventitia. Degeneration of these fibers occurs as the result of the inflammatory process and fibrosis. The author considers the formation of the thrombus merely the result of damage to the intima and believes it is not specific in the disease.

Braeucker²⁵ expresses a somewhat similar view. He believes that the inflammatory process in the wall of the vessel results in irritation

23 Ratschow, M. *Periphere Durchblutungsstörungen und Berufsschaden*, Verhandl. d. deutsch. Gesellsch. f. Kreislaufforsch., 1936, p. 220.

24 Yanovsky, M. *Sistema neuro-organo-vegetativo en el síndrome trombo-angitis tipo buerger, denominado neuroangitis fibrosa obliterante*, *Semana med.* 2: 968 (Oct. 8) 1936.

25 Braeucker, W. *Die Heilerfolge bei den Gefässerkrankungen an den Extremitäten*, Verhandl. d. deutsch. Gesellsch. f. Kreislaufforsch., 1936, p. 319.

of the adjacent nerve plexuses. Abnormal nerve impulses are initiated which result in reflex vasoconstriction. These views are not entirely new, but the emphasis which Yanovsky places on the involvement of the sympathetic fibers within the vascular walls may be important.

Parker and Allen²⁶ report an interesting case of an inflammatory disease involving the digital arteries in which there were the clinical characteristics of Raynaud's disease. They believe this was actually a case of thrombo-angitis obliterans.

Bircher²⁷ describes a typical case of this disease in which he believes alimentary intoxication and vitamin deficiency played important parts in the etiology. He seems to base these conclusions on the effects of treatment. He likewise considers the effect of tobacco and secondary infection of the gangrenous areas as important contributing etiologic factors in the subsequent course.

Telford,²⁸ in a general discussion of the condition, also emphasizes the fact that the typical pathologic condition may be obscured by a secondary infection which occurs in ulcers in gangrenous areas. He considers the disease rare in the upper extremities and comments on the fact that when the hands are involved the disease has usually made great progress in the legs.

The visceral manifestations of the disease continue to arouse considerable interest. Telford²⁸ cites again the case of a man aged 26 who died of coronary thrombosis and whose coronary arteries showed typical pathologic signs of thrombo-angitis obliterans. Cohen and Barron²⁹ review the literature on this subject and comment on the paucity of actual autopsy material. They found reports of only 15 cases in which thrombo-angitis obliterans involving the digestive tract was suggestive. In 2 of these the diagnosis was proved, in 2 it was doubtful and in the others it was presumptive. The authors believe that associated arteriosclerosis may replace the typical pathologic picture and that degenerative changes often take place in the vessels when the disease process is primarily that of thrombo-angitis obliterans. They report an additional case of presumptive thrombo-angitis obliterans in which the peripheral

26 Parker, R. L., and Allen, E. V. Organic Disease of the Digital Arteries Suggesting Thrombo-Angitis Obliterans and with the Clinical Features of Raynaud's Disease, *Proc. Staff Meet., Mayo Clin.* **12** 118 (Feb. 24) 1937.

27 Bircher, Willy. Ein Fall von Endarteritis obliterans, *München med. Wchnschr.* **84** 168 (Jan. 29) 1937.

28 Telford, E. D. Thrombo-Angitis Obliterans, *Lancet* **1** 549 (March 6) 1937.

29 Cohen, S. S., and Barron, M. E. Thrombo-Angitis Obliterans with Special Reference to Its Abdominal Manifestations, *New England J. Med.* **214** 1275 (June 25) 1936.

findings were conclusive, at operation the condition within the abdomen suggested the diagnosis but did not offer definite proof. The clinical picture was that of partial intestinal obstruction, colicky abdominal pain, vomiting, obstipation, distention and fever. These symptoms they regard as highly suggestive of involvement of the mesenteric vessels in the presence of peripheral disease. They believe that this condition should be considered an entity.

Saphir³⁰ reviews the literature reporting the autopsy observations in instances of Buerger's disease and notes the frequency, as have others, of the occurrence of coronary sclerosis and the relatively few patients who actually show the characteristic pathologic picture of thrombo-angitis obliterans. The patient whose case he describes in detail was a 35 year old man who died suddenly after an acute infection of the respiratory tract. For six years he had had symptoms of arterial disease involving the lower extremities but no evidence of cardiac disease. The autopsy revealed the combined picture of acute thrombo-angitis obliterans and arteriosclerosis. There were apparent transitions from the former to the latter, rendering it difficult to differentiate a thrombus arising on an atheromatous basis and a later stage of thrombo-angitis obliterans when organization of the thrombus had taken place. It seemed questionable whether the association of the two diseases was merely coincidental or the coronary sclerosis was the end-stage of earlier thrombo-angitis obliterans or had developed as an entirely different entity on the basis of thrombo-angitis obliterans. Saphir considers it possible that the inflammatory lesion in the vessel may have been a factor at least in the causation of the coronary sclerosis. This view has been expressed before, and Saphir's careful study lends weight to this opinion.

The coincidence of thrombo-angitis obliterans and Addison's disease in the same patient is reported by Silbert³¹. He raises the question of the possibility that the adrenal impairment is due to the vascular disease but concludes that this is not likely, because he considers visceral involvement a late manifestation of thrombo-angitis obliterans.

Kvale and Allen³² reviewed reports on 255 patients with thrombo-angitis obliterans and found that sudden arterial occlusion in the extremities appeared as the initial symptom of the disease in 11. It developed at various times during the course of the disease in 15 other patients in 10 of whom it was of such serious nature that amputation

30 Saphir, Otto. Thromboangitis Obliterans of the Coronary Arteries and Its Relation to Arteriosclerosis, *Am Heart J* **12** 521, 1936.

31 Silbert, Samuel. Thrombo-Angitis Obliterans and Addison's Disease in the Same Patient, *J A M A* **108** 551 (Feb 13) 1937.

32 Kvale, Walter, and Allen, Edgar V. Sudden Arterial Occlusion in Thromboangitis Obliterans, *Am Heart J* **12** 458, 1936.

was eventually necessary. The authors point out that the serious consequences of this complication are due to the fact that the blood supply has been previously so reduced that the limb cannot survive further reduction. As they point out, this complication has been emphasized by Buegei and others.

The patient described by McAuley³³ probably falls into the group presenting sudden occlusion as the initial symptom. The first symptoms of the disease in this patient appeared within twenty-four hours. The foot began to feel numb and cold in the morning and later in the day became extremely painful. The subsequent course was that of the rapid development of typical symptoms.

SPECIFIC AND NONSPECIFIC TYPES OF ARTERITIS

Periarteritis nodosa continues to be a disease of considerable interest. Case reports have been more frequent. The etiology is still uncertain.

Spiegel³⁴ reports on a series of 15 patients, giving the postmortem observations. More than half the patients had preceding illnesses in which hemolytic streptococci were the most common bacterial agents implicated. These illnesses included tonsillitis, sinusitis, scarlet fever, asthma and rheumatic fever. The usual histologic picture of widespread vascular reactions prevailed. Seven patients in the group had surgical complications involving the gastro-intestinal tract. Almost all had abdominal pain. The coronary arteries, as stated in previous reports, seemed to be most frequently affected. Twelve patients had polyserositis, and high leukocyte counts were noted (in 1 patient, 54,000). The predominating cell was the polymorphonuclear leukocyte, although strikingly high eosinophil counts sometimes were noted. Healing and prolonged remissions occurred. Cutaneous lesions were not uncommon. The disease occurred in association with gonococcal infection and meningitis in 1 case. Only 1 of the patients in this series showed typical manifestations of an allergic state. Cohen, Kline and Young,³⁵ in a discussion of this condition, report 3 additional cases in which severe asthma was a predominating symptom. They believe that periarteritis nodosa is a severe manifestation of clinical allergy.

The pathologic picture, in their opinion, is not to be distinguished from that of severe allergy in which reversible reactions of varying degrees and irreversible reactions occur. There are areas of scarring

33 McAuley, C. J. Thrombo-Angitis Obliterans, *Brit. M. J.* **1** 411 (Feb 20) 1937.

34 Spiegel, Rose. Clinical Aspects of Periarteritis Nodosa, *Arch. Int. Med.* **58** 993 (Dec.) 1936.

35 Cohen, M. B., Kline, B. S., and Young, A. M. The Clinical Diagnosis of Periarteritis Nodosa, *J. A. M. A.* **107** 1555 (Nov. 7) 1936.

alone, areas in which only allergic inflammation are noted and every conceivable combination of allergic inflammation and repair. They divide the patients into four general groups according to the symptomatology: (1) fever, splenomegaly, leukocytosis, severe anemia and marked emaciation, (2) polyneuritis and polymyositis, (3) renal type and (4) abdominal type, with epigastric pain, vomiting and diarrhea. Combinations of these often occur, but some one group seems frequently to predominate. They state: "The clinical diagnosis is not difficult to make if the clinician will consider every patient having severe allergy as presenting a potential case of periarteritis nodosa and will watch for symptoms and signs which may be explained on the basis of a temporary or permanent disturbance of the blood supply to an organ."

Boyd and Nussbaum,³⁶ in a general discussion of the disease, emphasize the widespread vascular involvement and the multiplicity of symptoms. They noted that bronchial asthma is often recorded in the previous illnesses. Gonococcic infections in a few instances seem to them to possess etiologic significance, but syphilis is no longer to be regarded as a factor. Inability to discover the etiology of suspected sepsis together with negative results of blood culture is suggestive of periarteritis nodosa.

Yardumian and Cohen³⁷ present the case of a woman aged 64 whose chief complaint was of pain in the legs for the preceding two months. The pain was bilateral below the knees and cramplike, but was present only when the legs were dependent, always disappearing when the legs were elevated. There were no changes in the color or temperature of the skin. This patient also had had asthmatic symptoms during previous years. Autopsy confirmed the diagnosis. In 1 of the cases reported by Cohen, Kline and Young a diagnosis of Raynaud's disease had previously been made, and periarterial sympathectomy had been performed. Bilateral cervical sympathectomy was performed later, and one thumb and the gangrenous tips of two fingers were removed.

The relation of allergy to this condition is interesting, and the frequency with which allergic states are mentioned in the histories has been suggestive.

Spiegel in 1 patient with asthma observed at necropsy multiple pulmonary infarcts due to small thrombosed vessels in the lungs which might be held accountable for the asthma. She questions whether allergy on a nonbacterial basis may be associated with the development of periarteritis nodosa.

36 Boyd, L. J., and Nussbaum, C. Some Clinical Aspects of Periarteritis Nodosa, *M. Clin. North America* **20** 973, 1936.

37 Yardumian, K., and Cohen, R. Robert. Periarteritis Nodosa with a Case Report, *Ann. Int. Med.* **10** 1582, 1937.

ARTERIOSCLEROSIS

The question of the relationship of disturbances in cholesterol metabolism to the etiology of arteriosclerosis is still debatable. Leary³⁸ considers as inadequate the evidence against cholesterol as the essential etiologic agent and believes that the disease of atherosclerosis is due directly to disturbances in cholesterol metabolism. Points of stress in the walls of the vessels determine the localization of the lesions. Apparently any mechanical factor which may interfere with the local nutrition of the vascular wall provides a place in which lipid deposits will appear. The lesions are primarily intimal, and variations in their character are determined by the age of the patient and by the duration of the lesions. In youth cholesterol gains entrance into the subendothelial tissues, where it is engulfed by lipophages. Young fibroblastic tissue is produced, and these cells engulf the lipid. This leads to its disappearance from the lesions. Repair with only a small amount of scarring follows. In middle-aged persons the process is similar, but the metabolic processes are slower. Collagen is formed, and scar tissue results. There is nutritional impairment in the scar tissue, and the deeper layers undergo necrosis. Scars are the typical lesions in this period. In old age cholesterol metabolism ceases entirely. The lipophages accumulate in masses, with inadequate nutrition and support, resulting in primary atheromatous abscesses. Calcification arises only after necrosis has developed. It is the terminal phase of the disease and marks the sites formerly occupied by living tissue.

Ochsner and Conner³⁹ review some of the literature on this subject and report a case of lipoidemia which seems to have been on the basis of a distinct anomaly of lipid metabolism. Marked atherosclerosis involved almost all the visceral arteries. There were no organic changes suggestive of the named lipid dyscrasias. The patient died of coronary thrombosis. The cholesterol in the blood plasma reached a level of 667 mg per hundred cubic centimeters. There was moderate hypertension. In addition to thrombosis of the coronary arteries, the splenic artery was almost completely occluded. There was atherosclerosis of the abdominal aorta, with extensive atheromatous formation. There were no significant lipid deposits in any other part of the body except the vascular system. The authors conclude that it is reasonable to believe that the disturbance in cholesterol metabolism was the primary manifes-

38 Leary, Timothy. Atherosclerosis. Etiology, *Arch Path* **21** 459 (April) 1936, Atherosclerosis. Special Consideration of Aortic Lesions, *ibid* **21** 419 (April) 1936.

39 Ochsner, H. C., and Conner, H. M. Lipemia Accompanied by Atheromatous and Occlusive Vascular Disease. Report of Case and Partial Review of the Literature, *Ann Int Med* **10** 258, 1936.

tation and that atherosclerosis was secondary. However, the possibility must be considered that the atheromatous changes and the lipoidemia were due to rupture of atheromatous abscesses.

Freyberg⁴⁰ conducted experiments with rabbits, feeding them diets high in vegetable protein, and failed to produce atherosclerotic changes. There was no disturbance in the cholesterol values of the blood except with undernutrition. The author believes that his experiments suggest that the atherosclerosis which developed in rabbits fed on diets rich in muscle meat was due to a nonprotein constituent of the diet and not to the protein itself.

Parhon and Ornstein⁴¹ say that arterial hypertension and hypercholesteremia are the two incontestable factors in the development of arteriosclerosis and atheromatosis. They believe that endocrine dysfunction is the basis for the disturbance in lipid metabolism, particularly thyroid disorders. They feel that it is rational to consider that hypercholesteremia should be treated by the use of thyroid, as the preventive measure for the development of arteriosclerosis. They report 5 cases in which they were able to control the cholesterol level of the blood by the administration of thyroid or thyroxin.

Eberhard⁴² found that when alcohol was administered to rabbits together with cholesterol, the blood values for cholesterol rose more rapidly and to higher levels than in those animals which were fed cholesterol alone. Duff⁴³ conducted experiments which showed that the lipid deposits occurred in spontaneous medial lesions of the aorta and that in control animals the spontaneous lesions failed to show the deposits. The lipid is deposited only at points of vascular injury.

Krafka⁴⁴ discusses the numerous etiologic theories in regard to arteriosclerosis. He believes that any theory of sclerosis must be universally applicable throughout all periods of life and to all grades of vascular structures, from the aorta to the smallest vessels. He believes that the mechanical factors are of the utmost importance. He has developed a theory of herniation of the intima, with irritational hyperplasia, as the principal cause of the development of arteriosclerotic changes in all classes of vessels. It accounts for the frequency of the disease in hypertension but does not exclude the occurrence of sclerosis under

40 Freyberg, R. H. Relation of Experimental Atherosclerosis to Diets Rich in Vegetable Protein, *Arch Int Med* **59** 660 (April) 1937.

41 Parhon, C. I., and Ornstein, I. Traitement preventif de l'arteriosclerose et de l'atherome arteriel, *Schweiz med Wchnschr* **65** 1164 (Dec 7) 1935.

42 Eberhard, T. P. Effect of Alcohol on Cholesterol-Induced Atherosclerosis in Rabbits, *Arch Path* **21** 616 (May) 1936.

43 Duff, G. L. The Nature of Experimental Cholesterol Arteriosclerosis in the Rabbit, *Arch Path* **22** 161 (Aug) 1936.

44 Krafka, Joseph. The Mechanical Factors in Arteriosclerosis, *Arch Path* **23** 1 (Jan) 1937.

conditions of low pressure. Interstices occur in the subendothelial fibers, a variable pressure is always present and herniation results. This provides a simple mechanism for the so-called intimal hyperplasia.

Sappington and Cook⁴⁵ made a comparison of the changes in the radial artery and those in the coronary and other visceral arteries. They believe that the Monckeberg type of sclerosis is entirely independent of, and unrelated to the presence or absence of, atherosclerosis except that both conditions are found in persons over 50 years of age. The anatomic condition of the radial artery has no bearing on visceral sclerosis. The lesions were found to be maximal in the coronary arteries and minimal in the radial arteries, with intermediate degrees of changes in the vessels of the brain, spleen and kidneys.

Kampmeier⁴⁶ found arteriosclerosis in 41.8 per cent of 239 Negroes less than 40 years of age. These men showed no evidence of nephritis, hypertension or heart disease. Syphilis was present in only 16. Arcus senilis was found in 85 per cent of the patients with peripheral arteriosclerosis under the age of 40, whereas it occurred in a low percentage of the nonsclerotic patients. Kampmeier believes this association to be significant and that the two diseases may be due to the same etiologic factor. He believes that the high incidence of degenerative vascular disease in the Negro race is to be accounted for on the basis of nutritional deficiency. Just what this deficiency may be is uncertain. He raises the question of vitamin deficiency as well as deficiency in protein and minerals. No cholesterol studies were reported in these cases.

Hallock⁴⁷ has confirmed previous conclusions that premature arteriosclerosis occurs commonly in young diabetic patients. Why this occurs in many persons and not in all is still obscure. He has determined the presence of vascular degenerative changes in his group by measuring the rate at which the pulse wave is propagated through the arterial tree. Measurements of the transmission of the radial pulse wave are particularly significant in determining the degree of vascular hardening.

THROMBOSIS AND EMBOLISM

Embolism into the peripheral arteries is said to be the least frequent location, and Bull's figures have been quoted in support of this statement.⁴⁸ Embolisms into the lungs, kidneys, spleen and brain are much

45 Sappington, S. W., and Cook, H. S. Radial Artery Change in Comparison with Those of Coronary and Other Arteries, *Am J M Sc* **192** 822, 1936.

46 Kampmeier, R. H. Arteriosclerosis and Arcus Senilis in Young Negro Male, *J Trop Med* **39** 164 (July 15) 1936.

47 Hallock, Phillip. Arteriosclerosis in Young Diabetics, *Am J M Sc* **192** 371, 1936.

48 de Takáts, Géza. Acute Arterial Occlusions of Extremities, *Am J Surg* **33** 60, 1936.

more frequent The work of McKechnie and Allen, reported last year, gives a complete description of the symptoms and findings De Takats points out that arterial embolism may have premonitory symptoms Numbness, coldness or tingling may appear days or weeks before the sudden complete vascular occlusion The symptoms are the result of the release of minute fragments from the central clot, which is about to break loose Peripheral thrombosis usually is clear in its differentiation from embolism, but occasionally it is impossible to separate the two conditions It has been observed in patients as a manifestation of sudden occlusion and the first symptom of widespread arterial disease Acute vessel spasm following trauma may also be mistaken for acute organic occlusion The same type of reaction may accompany acute thrombosis, phlebitis or lymphangitis and may be mistaken for embolism Thrombosis may also quickly follow incomplete occlusion resulting from embolism, so that even on surgical exposure it may be difficult to decide whether the condition represents primary embolism or thrombosis Reflectoric vessel spasms are an important accompaniment of embolism and may be the essential factor in the development of gangrene

Gutzeit⁴⁹ and Nicole⁵⁰ have independently discussed the question of gangrene resulting from the acute arterial spasm that may occur coincidentally with venous thrombosis The symptoms may appear suddenly, with the development of moist gangrene associated with edema which is present as the result of the venous thrombosis Surface temperature is said to be the most reliable factor in differentiating this condition from embolism In venous thrombosis the peripheral temperature is normal

Fatherree and Hines⁵¹ report a case of extensive dry gangrene of the digits and skin of the legs associated with thrombocytopenic purpura This condition followed an acute illness of two weeks' duration The cause of the vascular occlusion could not be definitely determined It was suspected that ergotism might be a factor, although infectious and allergic causes could not be entirely eliminated

Bargen and Barker⁵² report on a group of patients in whom more or less extensive gangrene resulted from multiple arterial and venous thromboses complicating chronic ulcerative colitis These patients all

49 Gutzeit, R Brand durch Venensperre, *Munchen med Wchnschr* **83** 1628, 1936

50 Nicole, R Arteriospasmus bei akuter Venenthrombose, *Schweiz med Wchnschr* **65** 676 (July 27) 1935

51 Fatherree, Thomas J, and Hines, Edgar A, Jr Symmetrical Gangrene of the Extremities Associated with Purpura, *Am Heart J* **12** 235, 1936

52 Bargen, J Arnold, and Barker, Nelson W Extensive Arterial and Venous Thrombosis Complicating Chronic Ulcerative Colitis, *Arch Int Med* **58** 17 (July) 1936

showed exceedingly severe types of the disease. The location of the involvement was chiefly in the large venous trunks, and the extent of the pathologic involvement seemed to be out of proportion to any changes which could be seen in the vascular walls. The inflammatory reactions seen in the pathologic sections seemed to be minimal. It is probable that the essential cause of the thrombosis was the combination of local infection, general toxemia, alterations in the blood and venous stasis. Three of the 6 patients in whom thrombosis occurred died.

Coakley and Klein⁵³ report a rare condition under the title of progressive postoperative gangrene of the skin. They review the literature on the subject and describe an apparently typical case following appendectomy in which there was extensive gangrene of the skin involving almost the entire abdominal wall. They consider this a clinical entity, although the cause is uncertain. In this particular case the onset was marked by the appearance of a boil. Later this lesion assumed the characteristics of a carbuncle, and finally a spreading infection of the skin developed which rapidly became gangrenous. Culture of material from the wound showed a profuse growth of nonhemolytic streptococci.

THE RAYNAUD SYNDROME

In the past few years the conception of the Raynaud phenomenon as a distinct clinical entity has gradually lost ground. This phenomenon has been recorded in such a variety of clinical states and success has been reported with such a variety of different types of treatment that the condition is much more often part of a syndrome than a distinct disease entity. It is true that in certain cases there is no evident associated or coincidental disease. The etiology is no nearer solution, and whether the fault lies in the peripheral vessels or in the central nervous system is still an open question. However, as was stated in a previous review of this subject, it appears that the fault or sensitized tissue may lie anywhere along the vasomotor tract from the central nervous system to and including the peripheral vessels. It seems relatively unimportant, since the end-result is the same, whether one considers that the fault lies in vessels which are oversensitive to normal stimuli or in an overactive sympathetic nervous system which produces excessive stimulation to the peripheral vessels. The effect of sympathectomy in either case would have essentially the same bearing. Some of these ideas are expressed in an admirable paper on the Raynaud phenomena by John H. Hunt⁵⁴. He critically reviews the subject, including the cases reported by Raynaud.

⁵³ Coakley, Walter A., and Klein, D. Progressive Postoperative Gangrene of Skin, *Am J Surg* **33** 287, 1936.

⁵⁴ Hunt, J. H. The Raynaud Phenomena. A Critical Review, *Quart J Med* **5** 399, 1936.

Hunt believes that the term Raynaud's disease would be better changed to the Raynaud phenomenon. He feels that Raynaud's disease is exceedingly rare and that the Raynaud phenomenon occurs in a wide variety of definite and indefinite disorders. He classifies Raynaud phenomena as follows:

A. When the Raynaud phenomenon occurs alone

1. In normal persons exposed to cold long enough to lower the temperature of the blood
2. Hereditary cold fingers
3. Idiopathic Raynaud's disease
4. After the use of vibrating tools and after local injury to the hands or feet

B. When the Raynaud phenomenon precedes, perhaps by several years, a condition of permanent coldness and cyanosis of the extremities

5. Sclerodactylia

C. When the Raynaud phenomenon is a temporary and often insignificant phase in the development of gross vascular disease of the extremities

6. Thrombo-angitis obliterans
7. Arteriosclerosis
8. Syphilitic arteritis
9. Rheumatic arteritis
10. Cervical rib
11. In certain cases of pulmonary tuberculosis, leukemia, polycythemia vera, lupus erythematosus, malaria, chronic arsenical poisoning and many others

This is an ill defined group in need of further subdivision. Hunt points out that as many as seven of these different conditions appear in the original Raynaud thesis.

By experimentation on himself Hunt was able to induce reactions which he believes satisfied all the requirements of the Raynaud phenomenon in a normal person. This was done by lowering the temperature of the blood to points below 35.5°C. As long as the blood or rectal temperature remained above this level the phenomenon could not be induced. The peripheral vasoconstriction which occurs when the body temperature falls several degrees is probably a protective mechanism which prevents too great a reduction in temperature. There is a type of mild vasomotor reaction occurring apparently in normal persons who manifest this sensitivity by blanching or numbness of one or two fingers when exposed to cold. Hunt classifies this as hereditary cold fingers. He calls it the simplest and commonest type of Raynaud phenomenon. Both sexes are affected, and usually other members of the family suffer from vascular disorders or have had chilblains. The author differs from other writers who believe that this type of reaction is a mild manifesta-

tion of Raynaud's disease. The onset usually occurs in childhood, often at about the eighth year. The three points which differentiate this condition from idiopathic Raynaud's disease are sex, family history and age at onset. The attacks vary from slight pallor to cyanosis and numbness of all the fingers of both hands. When the hands are warmed the fingers quickly recover their normal color. This disorder is not progressive, the condition often improves and may even disappear in adult life. It does not lead to any serious trouble or interfere with work. The treatment is essentially the avoidance of exposure of the hands to cold.

In discussing the third group Hunt states that Raynaud's disease is exceedingly rare. Only 1 patient in Raynaud's series can be included under this heading, and Hunt has been able to pick out only about 30 cases from the 500 reported in the English and American literature since the publication of Raynaud's original thesis. The average age at onset of symptoms is apparently 30, females are affected almost exclusively. The clinical picture which he regards as typical is the same as that defined by Allen and Brown. The conclusions of Hunt as to the effects of cooling, overcooling and emotion are essentially the same as those of Lewis. Hunt's description of the changes in color and temperature are also essentially similar to those of Lewis. Between the attacks the hands are usually normal. Nutritional changes, such as superficial sores on the finger-tips, deformities of the nails and the like, are all rare. The nervous system is normal, but many of the patients seem to be of a neurotic disposition. Without treatment the condition in most of these patients becomes steadily worse. Few improve under medical treatment, and he believes that sympathetic ganglionectomy helps all of these patients.

In discussing the fourth group Hunt states that the use of one of the many types of vibrating tools may cause the development of the Raynaud phenomenon. From the nature of the work it is chiefly men who suffer. The author's description is the same as that commonly given in this condition. Nutritional changes in the fingers are rare. The feet are normal, and the hand or hands which hold the tool are usually affected first. General examination usually shows entirely normal findings. When the patient gives up this work, the attacks of cyanosis diminish. He classifies under the same heading those patients in whom vasomotor reactions to cold develop after some local injury to a digit or part of the hand or foot. He states that in both of these types a local fault in the digital or palmar arteries due directly or indirectly to the trauma is an inviting explanation, but the exact cause is not clear.

Under the heading of sclerodactylia Hunt includes many of the conditions which are usually described as Raynaud's disease. This is to be sharply differentiated. He quotes Seller as saying that sclerodactylia occurs in two different conditions. In the first type the face, hands and

feet may be involved. The disorder usually begins with the skin of the finger-tips and spreads slowly upward, rarely reaching as far as the palm or the dorsum of the hand. The second type is the diffuse or true scleroderma, in which the process begins on the trunk and limbs and spreads distally down the arms so that the dorsum of the hand is involved before the fingers. Females are affected more often than males. When the Raynaud phenomenon occurs in this condition, cold is usually the precipitating factor for an attack, but emotion may sometimes bring it on. The character of the paroxysm is essentially the same as that of Raynaud's disease. Pain is often severe. In the early stages the thickening of the skin may be difficult to recognize, and the fingers may sometimes swell, only to shrink later in the course of the disease. Nutritional changes in the fingers are an important characteristic in this group. Small sores of the finger-tips and superficial gangrene without suppuration are characteristic. Small depressed scars occur which are sometimes tender. Deformities of the nails, shortening of the distal phalanges and whitlows are common. Scleroderma of the face is found to accompany sclerodactylia in about three fourths of the patients. In many of the patients the condition becomes steadily worse. In some it remains stationary and in a few patients attacks of asphyxia occur. In the patients with progressive involvement the hands become more and more fixed and crippled, and the attacks of cyanosis are of longer duration and more severe. In the end the extremities are permanently cold and blue, and the condition no longer satisfies the criteria of the Raynaud phenomena. While many authors have described the relationship between the Raynaud phenomenon and scleroderma or sclerodactylia, many cases of this disorder continue to be reported as Raynaud's disease. Hunt believes that in this condition the local fault will be identified in a microscopic study of the pathologic features of sclerodactylia. In the walls of the arterioles there is intimal thickening, with atrophy and fibrosis of the media and fibrosis around the vessels as well as cellular infiltration in the corium. There is dense fibrosis, with atrophy of the papillae, hair follicles and sweat glands.

The occurrence of vasomotor symptoms begins in the early stages in about a third of the patients with thrombo-angitis obliterans. Symptoms of this type, with intermittent pallor or cyanosis, may last for several months before the onset of claudication or rest pain. As the disease advances, these vasomotor phenomena of the Raynaud type disappear. Similar conditions occur in arteriosclerosis, and Hunt believes that attacks of cyanosis may frequently be found in arteriosclerosis.

The typical Raynaud paroxysm has been associated with both congenital and acquired syphilis. It is a working rule with Hunt to suspect the presence of syphilitic endarteritis whenever the Raynaud phenomena are associated with necrosis of the ears or nose or with hemoglobinuria.

The paroxysm in cases of this type probably results from local vascular injury. With antisyphilitic treatment the results are often excellent, and this no doubt accounts for the reports of the cure of Raynaud's disease with antisyphilitic treatment.

In rheumatic arteritis much the same series of events may take place. Typical Raynaud phenomena may occur, associated with rheumatic conditions following streptococcic infections. They usually subside when improvement begins.

In Hunt's opinion, most of the cases of cervical rib which have been reported do not fulfil the requirements for the Raynaud phenomenon. There are usually continuous and not intermittent vascular spasms.

On the last group, which appears to be an important one, Hunt is able to throw little light. In all these conditions typical Raynaud phenomena are occasionally seen. Why they occur is unknown. It is in this group that many new cases reported as Raynaud's disease belong. In addition to the diseases mentioned by Hunt, the group of endocrine disorders with Raynaud phenomena, arthritis and diseases of the central nervous system as well as arsenic intoxication may be placed.

Prinzmetal⁵⁵ reports on some interesting studies on what he calls the mechanism of circulatory insufficiency in Raynaud's disease in association with sclerodactylia. Contrary to Hunt, it is his opinion apparently that sclerodactylia is superimposed on Raynaud's disease, and when this occurs the ischemic process becomes gradually intensified, and gangrene occurs. In the form of the Raynaud syndrome associated with sclerodactylia the clinical symptoms, according to this author, are severe, and the vascular reactions differ from those of the typical Raynaud syndrome in that there are superimposed the mechanical effects of the changes in the skin which result in a constricting band which mechanically interferes with the flow of blood through the vessels of the fingers. This ischemia affects not only the larger vessels but the arterioles, capillaries and veins, and it is the capillary constriction particularly which probably is largely responsible for the impairment of nutrition in the tissues. Prinzmetal ingeniously devised a method by which the normal finger could be made to simulate and produce vascular reactions identical with those of actual sclerodactylia.

Sunder-Plassmann and Mueller⁵⁶ report on a patient with so-called Raynaud's disease in whom there were disturbances in both carbohydrate and calcium metabolism. They were able to control the paroxysm by injecting an anesthetic into the stellate ganglion and

55 Prinzmetal, Myron. Studies of the Mechanism of Circulatory Insufficiency in Raynaud's Disease in Association with Sclerodactylia, *Arch Int Med* **58** 309 (Aug) 1936.

56 Sunder-Plassmann, P., and Mueller, K. Morbus Raynaud und neuro-vegetative-hormonales System, *Klin Wchnschr* **16** 162 (Jan 30) 1937.

effecting bilateral removal of this structure. This was followed by a return to normal of both carbohydrate and calcium levels in the blood. They express the opinion that Raynaud's disease represents a disturbance of the entire autonomic nervous system, central as well as peripheral, and that the hormones associated with the neurovegetative system are equally disturbed. This case suggests the ones which have been reported by Garlock,⁵⁷ in which marked improvement occurred either after calcium management or after parathyroidectomy. Garlock states that most patients suffering from Raynaud's disease sooner or later show changes in the skin which come under the classification of scleroderma, and this is usually evident in the fingers and hands. He feels that the development of scleroderma is preceded by vasospasm of the same type as that which occurs in Raynaud's disease. This of course is in contrast to the definite ideas expressed by Hunt, who feels that the Raynaud phenomenon is part of the course of scleroderma. Garlock's views, as expressed in his recent publications, are essentially the same as those reported in the review of last year.

Linenthal⁵⁸ reports a case of Raynaud's disease with pulmonary complications, which is apparently one of scleroderma. Numerous instances of visceral fibrosis have been reported in association with scleroderma.

As another example of Hunt's group 2 is the case reported by Klinefelter⁵⁹ regarding the successful treatment of Raynaud's disease with estrogenic substance. This was obviously an example of Raynaud syndrome occurring in a patient with endocrine dysfunction, with symptoms of menstrual disorder with hot flashes. The Raynaud paroxysms disappeared when the menstrual cycle returned to normal.

Rechtman⁶⁰ adds 2 cases to the few which have been reported in males. These cases appeared to fulfil the requirements for the diagnosis of idiopathic Raynaud's disease.

Smithwick⁶¹ also reports cases in which scleroderma eventually developed after years in which the Raynaud syndrome was a prominent complaint. He also comments on extensive pulmonary fibrosis, with diminished vital capacity and excessive perspiration of the involved extremities in this group.

57 Garlock, J. H. Parathyroidectomy for Raynaud's Disease and Scleroderma, *S. Clin. North America* **16** 771, 1936.

58 Linenthal, H. Pulmonary Complications in Raynaud's Disease, *New England J. Med.* **216** 188 (Jan 28) 1937.

59 Klinefelter, Edmund W. Successful Treatment of Raynaud's Disease with Estrogenic Substance, *Arch. Dermat. & Syph.* **34** 887 (Nov.) 1936.

60 Rechtman, A. M. Raynaud's Disease in Man, *Ann. Int. Med.* **10** 549, 1936.

61 Smithwick, R. H. The Value of Sympathectomy in the Treatment of Vascular Disease, *New England J. Med.* **216** 141 (Jan 28) 1937.

Adson ⁶² includes under the heading of Raynaud's disease the typical phenomenon of vasospasm, which he says varies in degree from mild discomfort to ulcerative gangrene of the digits, with sclerodactylia and what he calls dactyl arthritis. He repeats the previous arguments on which he bases the assumption that the Raynaud phenomenon is the result of a fault in the central mechanism of the autonomic nervous system.

Vasospastic Disease Due to the Use of Vibrating Tools—Drenckhahn ⁶³ discusses this type of vasospastic disease and reports a group of cases in which the disorder developed in coal-miners who used picks. He believes that this vasospastic disease which occurs as the result of the use of vibrating tools, particularly in stonecutters and shoemakers, is produced in miners as the result of vibration in a particular type of patented pick. The symptoms which he describes as occurring in these men are identical with those of previous descriptions of this disorder. Hunt ⁶⁴ makes an additional report of 7 cases of this type of vasospastic disease occurring in riveters in a locomotive workshop. In these men the attacks of syncope occurred in winter only. They increased in severity and finally were present even in warm weather. The symptoms varied from light pallor of the finger-tips to cyanosis of the whole hand. If a finger was cut while in this state, little or no bleeding occurred. When warmth was applied, the fingers rapidly regained their normal color. It is interesting to note that emotion played no part in precipitating these attacks, nor did vibration alone without cold. Another interesting fact noted by Hunt is that symptoms did not occur among the men working with hot rivets. This is probably because there is less vibration induced by the riveting machine when hot rivets are used.

Mikkelsen ⁶⁵ draws attention to the occurrence of posttraumatic arteriospasm in the fingers. It follows injuries of various types and may involve even the hand. He describes 2 cases following Colles' fracture. He believes that conditions of this type may easily be confused with or mistaken for neuroses. Pain, coldness, pallor and unusual susceptibility to cold are important symptoms. Protecting the fingers from cold, splinting and bandaging are often effective forms of treatment.

62 Adson, Alfred W. Physiologic Effects Produced by Ablation of the Autonomic Central Influence. Various Forms of Sympathectomy in the Treatment of Diseases, *Surgery* **1** 425, 1937.

63 Drenckhahn, C. H. Vasospastic Disease of the Hands of Miners Due to Vibration, *Illinois M. J.* **70** 354, 1936.

64 Hunt, J. H. Raynaud's Phenomenon in Workmen Using Vibrating Instruments, *Proc. Roy. Soc. Med.* **30** 171, 1936.

65 Mikkelsen, O. Posttraumatiske arteriospasmer paa fingrene, *Hospitaltid* **80** 177 (Feb. 16) 1937.

PRIMARY IDIOPATHIC THROMBOPHLEBITIS

It is under this term that Barker⁶⁶ presents a careful study of the condition which has usually been recorded under the term thrombophlebitis migrans. The report covers a group of 79 patients in whom none of the known causes of thrombophlebitis and conditions which it sometimes complicates were present. There were no recognizable factors of abnormal venous stasis. He divides the patients into two groups. In one group the condition was recurrent and of the type of thrombophlebitis migrans, and in the other group there was no repetition of the episode. The disease was not limited by age or race, although the majority of patients were men. The frequency of recurrence was variable. The veins of both legs were involved in the majority of patients, although lesions appeared in both arms and in both legs. The lesions of the superficial and saphenous veins appeared to be inflammatory in all the patients and could be felt as firm indurated cords which were tender and showed surrounding inflammatory reaction. Fever was variable, pulmonary embolism was not uncommon and edema occurred in many of the patients. Special studies of the blood failed to reveal anything of significance, and culture of material from the thrombosed veins remained sterile. The group in which there was only a single episode presented much the same characteristics during the illness as did the group with recurrent episodes.

Although Barker recognizes the relationship of this disorder to thrombo-angitis obliterans, he feels that there are definite differences in the venous involvement. The entire absence of involvement of the arteries is important. The limitation as to age and sex is not so certain. Large veins are frequently involved. Pathologically there is less proliferation of connective tissue than in thrombo-angitis obliterans. The author feels that this is a definite clinical entity and that as yet no etiologic factor can be named.

Tomas⁶⁷ reports a case of axillary thrombophlebitis with the pathologic observations made after amputation for gangrene. The arteries appeared to be normal. All the veins were involved, with massive occlusion of the venous system of the arm. This represents a case of gangrene of purely venous origin. Infection was an essential factor.

SECONDARY THROMBOPHLEBITIS

In inflammatory conditions involving the veins, with thrombosis, or thrombosis occurring as the result of alterations in the blood or after

66 Barker, Nelson W. Primary Idiopathic Thrombophlebitis, *Arch Int Med* 58 147 (July) 1936

67 Tomas, L. A Contribution to the Pathology and Clinical Features of Thrombophlebitis of the Upper Extremities, *Arch ital di chir* 43 525, 1936

stasis, the phenomena are so varied and so well known that little can be said of them here. It is, however, interesting to note that Altschuler⁶⁸ reports on 2 patients with tuberculous thrombophlebitis of the lower extremities in whom there was no adjacent tuberculous disease. Only the intima was attacked. The inguinal glands were removed and examined, and no evidence of tuberculosis was obtained. This was apparently the only site of the tuberculous process in either patient. The author thinks that this type of involvement may not be as uncommon as now appears.

POLYCYTHAEMIA VERA AS A VASCULAR DISEASE

Norman and Allen⁶⁹ discussed polycythaemia vera from the standpoint of its vascular complications and report on a group of 98 patients. Vascular phenomena occurred in a large proportion of this group. In addition to myocardial infarction, angina pectoris, cerebral hemorrhage or thrombosis, intra-abdominal thrombosis, occlusive disease of the peripheral arteries and vasomotor neuroses occurred. The authors point out that this disease often occurs at the time of life when degenerative vascular disease is common and that thrombosis of both arteries and veins occurs in a much larger proportion of the patients than could ordinarily be expected. The actual incidence of degenerative vascular disease is also high. In some instances chronic occlusive arterial disease occurred which could not be distinguished from arteriosclerosis obliterans. The authors comment on the frequency of burning paresthesia simulating erythromelalgia. One patient presented symptoms suggesting the Raynaud syndrome. Vascular lesions also occurred with relative polycythemia, including such conditions as thrombo-angitis obliterans as well as arteriosclerosis. The authors believe that treatment of polycythaemia vera is important in order to prevent vascular complications.

ERYTHROMELALGIA

Mufson⁷⁰ agrees that erythromelalgia is a symptom complex dependent on minute vascular changes of unknown etiology. He made a careful study of 2 patients who exhibited this syndrome. Capillary studies and observations on capillary and venous pressures showed an exaggerated reaction to warmth, with dilatation and an increase of pressure in these vessels. He feels that this dilatation is the result of the absence of normal antagonistic vasoconstriction and that symptoms could be relieved for as long as a few days by the intravenous

68 Altschuler, E. Tuberculous Thrombophlebitis of the Lower Extremity, *Lancet* **1** 948 (April 25) 1936.

69 Norman, I. L., and Allen, E. V. The Vascular Complications of Polycythemia, *Am Heart J* **13** 257, 1937.

70 Mufson, Isidor. Clinical Observations in Erythromelalgia and a Method for Its Symptomatic Relief, *Am Heart J* **13** 483 1937.

infusion of epinephrine hydrochloride and even by the inhalation of a 1:100 solution. In 1 patient it seemed as if chronic alcoholism might have been a factor. The dilatation and increase in capillary pressure occurred coincidentally with the development of pain.

TREATMENT

That the treatment of peripheral vascular diseases has been well stabilized is shown by the large number of papers on this subject. Most of these recount experiences with methods that are well established and are largely reviews or summaries the subjects of which have been considered in previous reviews in this journal.

Subsequent reports⁴⁸ express satisfaction with the use of papaverine hydrochloride as a valuable aid in the management of cases of sudden arterial occlusion. This drug should be used in conjunction with other aids, including heat properly applied and of the right degree, together with negative pressure in overcoming the associated vessel spasm.

Berens⁷¹ reports most gratifying results in the treatment of thrombo-angitis obliterans with sodium thiosulfate and sodium iodide according to the ideas of Rabinowitz. The basis for this treatment was reviewed last year. The favorable results following the arterial injection of iodine-containing contrast mediums have been reported in the European literature. Beutel and Klein⁷² have given as many as thirteen injections to 1 patient. They believe that in some cases this injection treatment will postpone or prevent the amputation of an extremity when all other methods have failed. They state that the patient experiences a burning sensation which is accompanied with dilatation of the surface capillaries, as shown by capillaroscopy.

Ratschow¹³ regards the injection of neo-iopax or abrodial (the sodium salt of mono-iodomethane sulfonic acid) intra-arterially into patients with severe vascular disease as a method so efficacious that it cannot be ignored. He quotes previous workers on the subject and feels that in all cases of severe gangrene this method should be employed before amputation is performed. There have been no reports of the use of substances of this type in the American literature.

Ewald,⁷³ in discussing the therapy of embolism, points out the difficulties in the recognition of latent deep venous thrombosis. This dis-

71 Berens, S. N. Use of Sodium Thiosulphate and Sodium Iodide in Case of Buerger's Disease (Thrombo-Angitis Obliterans), *J. Chemotherapy* **13** 106, 1936.

72 Beutel, A., and Klein, O. Percutaneous Arteriography as a Therapeutic Method, *Med. Klin.* **32** 899 (July 3) 1936.

73 Ewald, C. Therapy of Thrombophlebitis and of Thrombo-Embolism, *Wien. med. Wchnschr.* **86** 537 (May 16) 1936.

order may appear with or without signs of inflammation. In order to prevent the detachment of the thrombus he emphasizes the importance of complete rest and proper position of the limb. The lower part of the leg should be supported so that the knees are bent, and elastic bandages should be carefully applied in order to prevent the release of a portion of the thrombus.

An interesting development in the mechanical treatment of vascular diseases is that reported by Collens and Wilensky⁷⁴. They have employed the principles of reactive hyperemia by the application of intermittent venous occlusion. They claim that this is in no way related to intermittent suction and pressure. Their procedure is based on the principle of reactive hyperemia. A pneumatic cuff is applied about the proximal portion of the extremity, and a pressure of from 60 to 80 mm. of mercury is applied in alternating periods of two minutes each. They report on the treatment of a group of 29 patients for whom no other treatment was used except rest in bed. The most outstanding results which they obtained were the complete and rapid relief from pain. Ulcers showed an unusual tendency to heal. They report on 1 patient with thrombo-angitis obliterans who had been under treatment by generally accepted methods for seven years without relief from pain or any influence on the state of the ulcer. At the end of twelve hours of treatment by intermittent venous compression there was some relief from pain. Within five days the patient was able to sleep without the use of a narcotic or sedative for the first time in many months. In eight weeks the ulcer completely healed. No mention is made of previous treatment by alternating suction and pressure. The authors report the relief from pain in less than twenty-four hours in all the five other patients with thrombo-angitis obliterans. In 23 patients with atherosclerosis obliterans, 13 of whom were diabetic, complete relief from pain was obtained in 17, partial relief in 5 and none in 2. When relief occurred it was apparent in from two to forty-eight hours of treatment. The authors believe that gangrene of 2 patients with diabetes was made definitely worse by this treatment, and the necessity for amputation was hastened. In 4 other patients healing occurred, and 5 more showed healing at the time of the report. Patients with intermittent claudication were uniformly relieved. In the patients with ulcer or gangrene they were able to obtain the greatest amount of relief by maintaining a pressure of from 40 to 50 mm. of mercury for periods of one hour alternating with one hour of rest. This is indeed an encouraging report, and the method deserves careful follow up.

⁷⁴ Collens, William S., and Wilensky, Nathan D. The Treatment of Peripheral Obliterative Arterial Diseases, *J A M A* **107** 1960 (Dec 12) 1936

The value and limitation of the use of alternating suction and pressure have apparently been well established. Relatively little change has been offered in regard to these factors. Almost all reports are encouraging, and it seems that this method is well established in its field of usefulness. The limitations have been discussed in previous reviews. Bierman⁷⁵ considers that the compression made around the leg by the cuff which is used to seal off the device in which the leg is placed is an essential defect. No matter how arranged, the cuff causes some embarrassment to venous circulation and to a lesser degree to the arterial circulation. Barker⁷⁶ is apparently not at all certain as to the general value of this method of treatment. He suggests that it has its place, particularly in the treatment of rest pain, acute arterial occlusion, frost-bite and mild ischemia.

Edwards⁷⁷ has devised a chamber for applying the proper degree of heat to the extremity in order that the proper local effect of warmth on the arterioles and smaller vessels may be obtained, as has been emphasized by Herrmann. He points out that locally applied warmth is capable of producing maximum vasodilatation and increases the effectiveness of suction. The local increase in metabolism caused by the raised temperature assists the process of healing.

Board⁷⁸ reports favorable results with the method. In his experience the most striking benefits have been obtained following the ligation of a large artery or sudden occlusion of the vessel. Frozen feet responded promptly if intensive treatment was begun before complete obliteration of the arterioles had taken place. He also has been disappointed in the treatment of thrombo-angitis obliterans.

Bloom and Porter⁷⁹ have been encouraged by their results. Patients suitable for suction and pressure treatment should be carefully selected and adequately supervised while under treatment.

Interesting observations on changes in the oxygen content of the blood after passive vascular exercise are reported by Veal and McCord⁸⁰. By means of these determinations they feel that the prognosis in some

75 Bierman, W. Diagnosis and Treatment of Peripheral Vascular Disease by Physical Agents, *New York State J Med* **36** 1405 (Oct 1) 1936

76 Barker, Nelson W. Physical Agent in Treatment of Circulatory Diseases of Extremities, *Arch Phys Therapy* **17** 554, 1936

77 Edwards, E. A. Treatment of Organic Arterial Obstruction by Alternating Suction and Pressure, *J A M A* **108** 626 (Feb 20) 1937

78 Board, O. P. Passive Vascular Exercises in Treatment of Obliterative Vascular Disease, *South Surgeon* **5** 255, 1936

79 Bloom, Nathan, and Porter, William B. Problems in the Diagnosis and Treatment of Peripheral Vascular Disease, *Virginia M Monthly* **64** 7, 1937

80 Veal, J. Ross, and McCord, William M. Blood Oxygen Changes After Passive Vascular Exercise of the Extremities, *Proc Soc Exper Biol & Med* **36** 9, 1937

cases can be predicted. An increase in oxygen saturation of either the superficial or the deep venous blood or both after one hour's trial indicates that some improvement will follow this form of therapy. When there is no change or fall in oxygen saturation the prognosis is poor. They note a wide discrepancy between the changes in the oxygen content of blood from deep and that from superficial vessels after treatment with suction pressure.

Theis and Freeland⁸¹ have also made extensive studies on the effect of treatment with alternating positive and negative pressure on the temperature of the venous blood of the skin. The temperature of the skin was taken under controlled conditions before and after each period of treatment. Analyses of the venous blood of the extremities for oxygen and carbon dioxide were made before and one hour after treatment with suction and pressure to both lower extremities and after heat at 45 C had been applied to the upper extremities for direct and indirect effects. In addition the authors made tests of the body metabolism and the oxygen consumption per minute before and one hour after treatment with alternating positive and negative pressure to both lower extremities and with heat applied to both upper extremities to increase the circulation of blood. They state that in their experience this procedure is the most effective means of relieving the pathologic changes which take place in the tissue owing to deficient circulation. They believe that the beneficial effects of this method of treatment are on the physiologic basis of increased tissue metabolism. The heat produces an increased blood flow, and the pressure treatment increases the exchange of oxygen and carbon dioxide in the tissues. Ordinarily no estimate can be made of the permanent effect of treatment by analyses of the exchange of oxygen and carbon dioxide in the tissues. Readings of the peripheral temperature are of value in determining how frequently and how intensively the treatment should be given. The authors think that the respiratory function of the skin may be an important factor in the success of pressure treatment. Keeping the skin soft and pliable probably aids in the absorption of oxygen from the air and the elimination of carbon dioxide. The oxidation process which is increased during treatment with positive and negative pressure may account for the increased temperature of the skin. Vasodilation as the result of direct or reflex heat is more effective in increasing peripheral circulation, but apparently it has little effect in increasing metabolism in the tissues and only increases the available supply of oxygen. The combination of these methods is of greater clinical value than is either method alone.

⁸¹ Theis, Frank V., and Freeland, M. R. *Peripheral Circulatory Diseases*, J. A. M. A. **107** 1097 (Oct 3) 1936.

A CRITICAL REVIEW OF THE LITERATURE ON SURGICAL TREATMENT

BY DR DE TAKATS

Contributions published since my last review can again be grouped as dealing with (1) attempts to improve the circulation, (2) attempts to relieve pain and (3) methods of amputation⁸²

REMOVAL OF VENOUS THROMBI

Lawen⁸³ reports on 3 patients from each of whom a venous thrombus was extracted shortly after its formation (one subclavian thrombus and two iliofemoral thrombi) Not only does the concomitant arterial spasm disappear, but the venous return is markedly improved Further observation will be necessary to establish the indications, the optimal time for this procedure and the possible hazards of pulmonary embolism Vascular and nutritional disturbances following venous thrombosis in certain patients have been relieved by stripping the vein from the surrounding exudate or scar tissue, which is a simpler procedure⁸⁴

ARTERIECTOMY

Leriche and his co-workers⁸⁵ have republished their work on arterial excision in patients suffering from organic arterial occlusion, which was previously reviewed Relief from symptoms was obtained in 43.6 per cent of the patients The authors state that the operation is not as satisfactory as lumbar sympathectomy, but it involves much less risk Leriche emphasizes again that an obliterated artery ceases to function as a carrier of blood and becomes a diseased plexus of sympathetic nerve fibers which maintain vascular spasm While this is an important and fruitful principle and deserves consideration in all types of arterial obstruction, his results with arteriectomy are not encouraging In the occasional case of traumatic or infectious thrombosis or instead of simple arterial ligation, arteriectomy may prove to be of great value

82 No attempt has been made to offer a complete bibliography Articles have been selected which contain new trends of thought or which crystallize previously suggested ideas

83 Lawen, A Ueber Thrombektomie bei Venenthrombose und Arteriospasmus, *Zentralbl f Chir* **64** 961 (April 24) 1937

84 de Takats, G Reflex Dystrophy of the Extremities, *Arch Surg* **34** 939 (May) 1937

85 Leriche, R, Fontaine, R, and Dupertuis, S M Arteriectomy, with Follow-Up Studies on Seventy-Eight Operations, *Surg, Gynec & Obst* **64** 149, 1937

EMBOLECTOMY

A thorough and instructive report on the late results of embolectomy is given by Hindmarsch and Sandberg,⁸⁶ 77 per cent of the patients suffered from chronic heart disease, and 6 per cent had undergone an operation on childbirth. When embolectomy was performed within the first ten hours after the onset of symptoms, 58 per cent regained normal circulation, 35.7 per cent of those operated on after the elapse of more than ten hours obtained a good functional result. All axillary and brachial embolectomies were successful. Two thirds of the patients whose extremities were saved died within ten years, the condition of the heart determining the outcome.

Pain, the early symptom of arterial embolism, is analyzed by Sir Thomas Lewis.⁸⁷ In embolism of an artery of a limb, pain and tenderness may occur at the site of the clot as a late symptom, but the early pain is not due to the impact of the clot, it is due to ischemia distal to the obstruction, chiefly in the muscles of the limb. Thus, embolism or thrombosis gives rise to pain when it affects muscular organs, like the limb, the heart or the bowel, but not when its effects are confined to nonmuscular organs, like the brain, the lung or the spleen.

In a lecture on embolism of an artery Nystrom⁸⁸ summarizes his vast personal experience and that of the group of Swedish surgeons concerning the early diagnosis and treatment of peripheral arterial embolism. He strongly believes in the early exposure of the occluded artery and offers a number of helpful technical suggestions. Half of his 32 patients operated on within the first ten hours were discharged with a restored circulation. Less favorable were the data on results collected from reports of 382 cases, the total Swedish material. The late results were as follows: Twenty per cent of the patients were discharged with a restored circulation, 20 per cent were discharged after amputation and 60 per cent died. In this country those who are interested in vascular surgery seldom see a patient for whom embolectomy is suitable, as the favorable time for operation is frequently missed. It is encouraging to note, however, that in a recent paper from the Cincinnati General Hospital, Herrmann⁸⁹ could report on 53

86 Hindmarsch, J., and Sandberg, I. Forty-Five Embolectomies, *Acta chir Scandinav* 78 81, 1936.

87 Lewis, T. Pain as an Early Symptom of Arterial Embolism and Its Causation, *Clin Sc* 2 237, 1936.

88 Nystrom, G. Lectures on Embolism and Other Surgical Subjects, Baltimore, Williams & Wilkins Company, 1936.

89 Herrmann, L. G. Experiences with the Conservative Management of Acute Arterial Occlusion, read at the Thirteenth Annual Meeting of the American Heart Association, Atlantic City, June 7, 1937.

patients with acute arterial occlusion, roughly half of whom arrived at the hospital within twelve hours. With a combination of heat, vasodilation and suction and pressure therapy the extremity was saved in more than half the cases. This result is better than any other reported after embolectomy. The next few years will show whether the limbs saved by conservative measures will be as useful and painless as the ones in which embolectomy has reestablished the major arterial pathways. The time factor is so important that further education of the general medical profession seems indicated.

Increasing interest in the influence of climatic conditions on vascular accidents is reflected in a number of articles. A review of these with a number of clinical correlations is presented in Petersen's monographs on the patient and the weather. In his recent volume on cardiovascular and renal disease he⁹⁰ again emphasizes the significance of pressor episodes and the associated rôle of anoxia brought about by meteorologic conditions. As Bartsch⁹¹ states, the present evidence does not allow one to postulate that an operation should be carried out only in "anticyclonic" weather, but if confirmed on a larger material it may point in that direction. Certain it is that every one dealing with data on arterial and venous thromboses must be impressed with certain seasonal and climatic influences. These observations, however, will obtain clinical significance only if simple practical methods of avoiding or buffering these pressor episodes can be worked out.

ARTERIOVENOUS ANEURYSM

The replacement of a long arterial segment with a venous transplant has been reported in 2 cases⁹². In each patient a large traumatic aneurysm necessitated an extensive loss of a major arterial trunk, which was successfully replaced by a transplant of a long segment from the long saphenous vein. This is a principle which has been promulgated from time to time, but few permanent end-results have been reported. Plugging of an aneurysmal sac with a pedicled muscle flap and repair of an arterial wound with a muscle flap rolled around the vessel have been experimentally and clinically studied by McNealy and Shapiro,⁹³ and the results seem most encouraging.

90 Petersen, W. F. *The Patient and the Weather. I. Cardio-Vascular-Renal Disease*, Ann Arbor, Mich., Edwards Brothers, Inc., 1937, vol. 4.

91 Bartsch, W. *Embolie und Wetter*, Schweiz. med. Wchnschr. **66** 1209 (Nov. 28) 1936.

92 Karitzky, B. *Gefassverletzungen und ihre Behandlung*, Zentralbl. f. Chir. **64** 8 (Jan. 2) 1937.

93 McNealy, R. W., and Shapiro, P. F. *Arterial Repair by Muscle Transplants*, Surgery **2** 61, 1937.

A case of traumatic arteriovenous fistula is reported by Dry and Horton⁹⁴ in which there was spontaneous closure after twenty-five years. While the affected limb was larger and longer, there was no intermittent claudication. Such a case has not been previously recorded. The Brianham sign—bradycardia following pressure over the arteriovenous fistula—is analyzed by Tournade and Curtillet,⁹⁵ who give two possible explanations. The sign, which had really been described by Nicoladoni long before Brianham made his report, may be due to a depressor reflex mediated through the vagus nerve or to an alternating pulse due to the sudden rise in general blood pressure.

CERVICAL RIB AND THE SYNDROME OF THE SCALENUS ANTICUS MUSCLE

Symptoms similar to those produced by a cervical rib but due to a tight scalenus anticus muscle are discussed by Flothow⁹⁶ and by Craig and Knepper.⁹⁷ According to Craig and Knepper, the symptoms result from compression or irritation of the brachial plexus and compression of the subclavian artery. Compression may be due to the presence of a cervical rib, an abnormally low position of the shoulder, a high fixation of the sternum and ribs, a low origin of the brachial plexus or elevation of the first rib from spasm of the scalenus muscle, which, in turn, is brought about by irritation of the plexus. Resection of the anterior scalenus muscle is usually all that is necessary, but when there is evident pressure from a cervical rib or its tendinous attachment, resection of the rib or its attachment should be carried out. In my experience these patients have frequently been said to have Buerger's disease, Raynaud's disease or a vegetative neurosis. That many of them are neurotic is more the result than the cause of definite organic findings, but a certain constitutional inferiority may be present.

Lindgren⁹⁸ reports on a patient who had an abnormally high and bulbous first thoracic rib which caused circulatory disturbances in the corresponding arm. Section of the anterior scalenus muscle and removal

94 Dry, T. J., and Horton, B. T. Traumatic Arteriovenous Fistula Involving the Right Femoral Artery and Vein. Spontaneous Closure, *Arch. Surg.* **33**: 248 (Aug.) 1936.

95 Tournade, A., and Curtillet, E. L'anévrysme artério-veineux expérimental. Note complémentaire sur l'épreuve de Brianham, *Compt. rend. Soc. de biol.* **122**: 15, 1936.

96 Flothow, P. G. Cervical Rib and Anterior Scalenus Syndrome, *West. J. Surg.* **44**: 570, 1936.

97 Craig, W. M., and Knepper, P. A. Cervical Rib and Scalenus Anticus Syndrome, *Ann. Surg.* **105**: 556, 1937.

98 Lindgren, S. Vascular Disease of Upper Extremity with Abnormality of First Thoracic Rib, *Acta chir. Scandinav.* **79**: 81, 1936.

of the anomalous rib did not give relief. It was found that the patient had an aneurysm of the subclavian artery distal to the compression and segmental obliteration of the brachial artery, demonstrated by arteriography. This condition would be suitable for local arterial excision, as advocated by Leriche⁸⁵

SYMPATHECTOMY

Experimental work on the rôle of the vegetative nervous system on peripheral circulation has continued during the past year. On a large series of dogs Albert and Dumont⁹⁹ used arteriography to study the effect of various types of sympathectomy. They found that the removal of the entire lumbar chain with the first sacral ganglion gave the greatest enlargement of the visualized vascular bed. Unfortunately, these were all acute experiments, and no late results are reported.

Bulbring and Burn¹⁰⁰ found in dogs that the vessels in the skin of the hindlimb receive no dilator sympathetic supply but that the muscles do. The dog's ear is different, because after paralysis of the vasoconstrictors with ergotoxine, stimulation of the sympathetic nerve causes dilatation of the aural vessels. Surgeons performing sympathectomies will be reminded by this article that vasodilators are carried in the sympathetic nerves, although obviously the major vasodilator outflow is through the posterior root ganglions. The vasodilator reactions, dependent on intact spinal ganglions, have been studied by Wybauw¹⁰¹. When the spinal ganglions were removed from cats and postganglionic degeneration occurred, there resulted no hyperemia after exposure to cold. This reaction is due to an axon reflex regulated by vasodilators the trophic cell of which is in the posterior root ganglion. Section of the posterior root proximal to the ganglion does not abolish this reflex.

The absence of these axon reflexes, previously studied by Sir Thomas Lewis, well explains the formation of "trophic" ulcers in areas devoid of normal sensation. It also indicates that sympathectomy for trophic ulceration is of no avail.

In a significant contribution by Freeman, Shaw and Snyder¹⁰² a report is made of studies of the blood flow through the hand. A reduc-

99 Albert, F, and Dumont, P. La chirurgie du sympathique lombaire. Etude arteriographique experimentale, *Rev belge sc med* **8** 445, 1936

100 Bulbring, E, and Burn, J H. Sympathetic Vaso-Dilatation in Skin and Intestine of Dog, *J Physiol* **87** 254, 1936

101 Wybauw, L. Rôle des ganglions rachidiens dans le mecanisme des reactions vasodilatatrices cutanees au froid et au chaud chez le chat, *Compt rend Soc de biol* **122** 456, 1936

102 Freeman, N E, Shaw, J L, and Snyder, J C. Peripheral Blood Flow in Surgical Shock. Reduction in Circulation Through Hand Resulting from Pain, Fear, Cold, and Asphyxia with Quantitative Measurements of Volume Flow of Blood in Clinical Cases of Surgical Shock, *J Clin Investigation* **15** 651 (Nov) 1936

tion was found to result from pain, fear, cold and asphyxia. The authors point out that the arterial blood pressure does not necessarily indicate the adequacy of blood flow through the tissues, in fact, the blood pressure may be increased by epinephrine or ephedrine only at the expense of the nutrition of tissues. In the sympathectomized limb there was an increase of blood flow after partial asphyxia, whereas in the normal limb the results were variable. Observations on patients for each of whom one limb had been sympathectomized have shown that a stimulus which normally produces reflex vasoconstriction may result in a paradoxical increase of pulsations in the sympathectomized extremity.¹⁰³

By far the most important contribution of the year to the experimental surgery of the sympathetic nerves is that of Ascroft.¹⁰⁴ He studied the early and late effects of the division of the vasomotor fibers in the rhesus monkey. Cutaneous temperatures were used to measure the rate of blood flow. Preganglionic operations were more effective in producing chronic vasodilatation than were postganglionic sections, and it seems rational in all cases to replace postganglionic sympathectomy by preganglionic division. In man all preganglionic fibers may be interrupted to the upper extremity by dividing the thoracic sympathetic chain just below the second ganglion and by severing connections to the second thoracic nerve. Horner's syndrome is thus avoided. On the lower extremity it might be well to leave the fourth lumbar ganglion intact, removing only the second and the third, for no white ramus reaches the fourth ganglion, and it gives off a gray ramus carrying postganglionic vasomotor fibers.

This work reemphasizes and corroborates the disadvantage of sensitizing vessels to various stimuli when postganglionic degeneration occurs. As mentioned in the last two reviews, the work of J. C. White and E. D. Telford points to preganglionic section as the method of choice. Although a certain amount of sensitization develops after this type of procedure, both experimental and clinical evidence indicate that this procedure is preferable. My limited experience is definitely in favor of preganglionic section.¹⁰⁵

Some evidence is gradually accumulating that even after complete sympathectomy peripheral vasoconstrictor mechanisms exist which maintain vascular tonus and blood pressure. Thus, Wilson, Roome and Grimson¹⁰⁵ studied the blood pressure of completely sympathectomized

103 de Takáts, G. The Effect of Sympathectomy on Peripheral Vascular Disease, *Surgery* **2** 46, 1937.

104 Ascroft, P. B. The Basis of Treatment of Vasospastic States of the Extremities. An Experimental Analysis in Monkeys, *Brit J Surg* **24** 787, 1937.

105 Wilson, H., Roome, N. W., and Grimson, K. Complete Sympathectomy. *Ann Surg* **103** 498, 1936.

dogs and found that it remained at a higher level than would be expected after the withdrawal of all vasoconstrictor impulses. They suggest the possibility of a peripheral vasoconstrictor mechanism. This is in line with Hirt's¹⁰⁶ view, reemphasized by Starlinger,¹⁰⁷ that beside the main efferent sympathetic pathways there is an accessory pathway through the spinal ganglion from both anterior and posterior roots which does not enter the sympathetic chain. The histologic evidence of a widespread nervous network, with automatic activity when disconnected from the cord, has been repeatedly discussed by Philip Stohr Jr.,¹⁰⁸ who believes that the two neuron theory of Langley is incorrect and that the sympathetic nervous system consists of a massive syncytial network of fibers and ganglions. These ganglions not only are present in the cord and in the sympathetic ganglions but are scattered in the periphery. They are capable of regenerating fibers, of automatic function and of reflex activity. Should this revolutionary theory be correct, there is still a marked benefit to be derived from sympathectomy. Central stimuli and spinal reflexes will not affect blood flow. In my experience the saturation of venous oxygen rises permanently, and blood flow is more even, being unaffected by many thermal and emotional stimuli which act through the central nervous system.

In regard to indications for sympathectomy, Pozniakoff and Kohan¹⁰⁹ feel that sweating of the limb is an indication of hypertonus of the sympathetic nervous system and that in a patient affected with Buerger's disease a sweating limb is suitable for sympathectomy whereas a dry one is not. Uprus, Gaylor and Carmichael¹¹⁰ subjected the test of reflectoric thermal effects to a searching analysis and found that the time of onset of vasodilatation in the limbs of a subject whose blood temperature is not rising rapidly should not be accepted as an indication of a disturbance of a nervous mechanism. They point out that the time of onset of vasodilatation is dependent on local temperature, the posture of the limb and the rapidity of the rise of the temperature of the blood. It seems from this work that the slow rise in the

106 Hirt, A. Ueber den Aufbau des Spinalganglions und seine Beziehungen zum Sympathicus, *Ztschr f d ges Anat (Abt 1)* **87** 275 (Sept 12) 1928

107 Starlinger, F. Zum Fernergebnis der Behandlung drohender Gangran der unteren Gliedmassen durch die Resektion des lumbalen Grenzstranges, *Mitt a d Grenzgeb d Med u Chir* **44** 203, 1936

108 Stohr, P., Jr. Bemerkungen zur Gefassinnervation, *Zentralbl f Chir* **61** 2 (Jan 6) 1934

109 Pozniakoff, L., and Kohan, A. Examen des reflexes vegetatifs dans l'endarterite obliterante, *Rev de chir* **75** 5, 1937

110 Uprus, V., Gaylor, J. B., and Carmichael, E. A. Vasodilatation and Vasoconstriction in Response to Warming and Cooling the Body. Criticism of Methods, *Clin Sc* **2** 301, 1936

cutaneous temperature following the application of heat to other parts of the body does not necessarily indicate that vasoconstrictor influences are being overcome

Leriche and Fontaine¹¹¹ reported the result of 1,199 operations on the sympathetic nervous system before the German Surgical Congress of 1936. There were 261 cervical sympathectomies, with 1 death from pneumonia, and 178 lumbar sympathectomies, with 6 deaths, a mortality of 3.3 per cent. Of the 6 deaths, 2 were due to pulmonary embolism and 1 each was due to infection of the wound, streptococcal peritonitis, cerebral hemorrhage and cardiac disease. Studying their indications and results, one must conclude that Leriche is becoming more conservative and that 4 of these deaths occurred in patients who had subacute phlebitis or arteriosclerosis and for whom the operation was not indicated. Leriche states that high lumbar sympathectomy, with removal of the first lumbar ganglion, gives better results than when the second and third ganglia are removed. In regard to sympathectomy versus arterial resection, he feels that resection is more successful in arteriosclerotic patients, whereas sympathectomy gives better results in Buerger's disease. As stated in my previous reviews, arterial resection can have only a limited indication, and its extensive use in arteriosclerotic patients does not seem logical.

In an excellent clinical lecture based mainly on personal observations J. C. White¹¹² reviews the surgical treatment of the sympathetic nervous system. These procedures are just emerging from the stage of trial and error, partly as the result of an accumulation of clinical evidence but also as the result of a better understanding of the function of these nerves and the development of diagnostic methods. In regard to peripheral vascular diseases, White and Smithwick have performed 18 lumbar sympathectomies for Raynaud's disease, all of which have been successful. The 58 patients who had sympathectomy for the upper extremity, however, have not shown the same amount of improvement. In the first series of 10 cases the upper two thoracic ganglia were removed. This proved to be an inadequate procedure. In the second series the extent was increased to include the inferior cervical ganglion. After early complete vasodilatation there was recurrence of spasms, although the hands remained dry. In the third series of 28 cases preganglionic section was performed by cutting the thoracic chain below the third ganglion and severing the communicant rami to the second and third intercostal nerves. Observations over a period of

¹¹¹ Leriche, R., and Fontaine, R. Einige Bemerkungen über 1199 Operationen am Sympathicus, *Arch. f. klin. Chir.* **186** 338, 1936.

¹¹² White, J. C. Recent Developments in Surgery of Sympathetic Nervous System, *New England J. Med.* **216** 91 (Jan. 21) 1937.

one and one-half years indicate that the lasting increase in blood flow in the arm can be as great as that in the leg. In scleroderma and sclerodactylia, in the late stages of poliomyelitis, in hyperhydrosis and in Buerger's disease valuable results have been obtained when the patients have been well selected. The author limits his indications for sympathectomy in Buerger's disease and advises its use for 12 patients in whom crushing of the peripheral nerves has been followed by regeneration and in whom vasospasm again has become a complicating factor.

Telford²⁸ has now performed lumbar sympathectomy on 112 patients suffering from Buerger's disease. In half the patients the results were good, in one-fourth only fair and in the remaining fourth unsatisfactory. He examined 22 patients who were operated on not less than three years ago in regard to the progress of the disease. Sixteen of the 22 were well, and 6 showed some degree of deterioration. Of these 6, 4 have required low amputation and 2 have had recurrent attacks of phlebitis. Unfortunately no mention is made of the type of postoperative treatment, the removal of foci and other conservative measures. Telford believes that sympathectomy is still the most hopeful of all the treatments that have been advocated.

Sympathectomy would undoubtedly gain more favor among the medical profession if it were performed with strictly limited indications and if the results were carefully followed from year to year. In Raynaud's disease lack of marked structural changes and absence of sclerodactylia have responded favorably, in Buerger's disease one should postulate a definite collateral reserve, absence of acute inflammation or arteriolar destruction and a poor response to conservative treatment. In anterior poliomyelitis moderate paralysis limited to one extremity, evidence of vasospastic phenomena and an age preferably between 6 and 10 years are the indications.¹⁰³ Among patients with reflectoric nutritional disturbances, commonly called reflex osseous atrophy, traumatic vessel spasm and traumatic edema, those with severe involvement who are resistant to rest, moderate exercise and physical therapy have done surprisingly well after interruption of the reflex arc by local excision of the irritating focus or by sympathectomy.⁸⁴ These reflectoric vascular disturbances need further study and may explain a number of obscure phenomena that have been "dumped into the wastebasket of vegetative neuroses."

AMPUTATION

In spite of the increasing interest in the early conservative treatment of peripheral vascular disease, amputation will always be necessary to relieve intractable pain, to remove a part hopelessly lost and to

restore economic efficiency of the patient. Blencke¹¹³ has studied the late results of 372 amputations which he has performed, mostly on soldiers injured in the World War. His technical advice need not be reviewed here except to state that he does not believe in direct weight bearing and that he reports on a number of late reamputations of seemingly excellent stumps. Crossan¹¹⁴ believes in a two stage amputation for diabetic gangrene, a simple guillotine amputation is made about 2 handwidths below the tibial tubercle, and a few weeks later secondary closure is made.

The use of a polyvalent serum for gas gangrene is reported by Bates¹¹⁵. For a group of 16 patients with gas gangrene treated without serum, the mortality was 50 per cent, for another group of 16 for whom serum was an essential part of the treatment, the mortality was 16 per cent. Bates advocates the preoperative prophylactic use of serum for patients who are to undergo amputation for diabetic or arteriosclerotic gangrene. This, with other prophylactic measures, is undoubtedly decreasing the mortality following amputation throughout the country. It is one of the future tasks of reconstructive surgery to devise suitable effective artificial limbs. No progress has been made in this field for a long time.

113 Blencke, A. Unsere Amputierten der letzten 3 Jahre vom Standpunkt des Prothesenbauers betrachtet, *Zentralbl f Chir* **63** 2299 (Sept 26) 1936

114 Crossan, E. T. Two Stage Amputation for Diabetic Gangrene of Leg, *Am J Surg* **33** 18, 1936

115 Bates, M. T. Gas Gangrene. Review of Thirty-Two Cases with Special Reference to Use of Serum, Both Prophylactic and Therapeutic, *Ann Surg* **105**: 257, 1937

News and Comment

ACADEMY OF PHYSICAL MEDICINE

The Fifteenth Annual Meeting of the Academy of Physical Medicine will be held at the Hotel Walton, Philadelphia, on Oct 19, 20 and 21, 1937

The academy, which is international in scope, will present a scientific program based on reports of the most recent research and practice of the various specialties. In addition to the lectures, demonstration clinics will be held at the hospitals of the University of Pennsylvania, Jefferson Medical College and Temple University.

A copy of the program may be had by addressing the chairman of the Committee on Program and Publication, William D. McFee, M.D., 41 Bay State Road, Boston.

CORRECTION

In the article by Dr. Cecil James Watson, "Studies of Urobilinogen. II. Urobilinogen in the Urine and Feces of Subjects Without Evidence of Disease of the Liver or Biliary Tract," in the February issue (*ARCH. INT. MED.* **59**: 196, 1937), the word "evaluation" was omitted after the word "permit" near the end of the eighth line from the top of page 197.

Book Reviews

Adiposita e Magrezze patologiche Lavori del XLII Congresso di medicina interna By Prof Francesco Galdi, of Pisa Pp 288 Rome Luigi Pozzi, 1936

This two hundred and eighty-eight page work is a laborious study of seventeen obese and ten underweight patients. The diagnostic categories into which the conditions noted were placed included Frohlich's syndrome, diencephalohypophysial obesity, thyroid obesity, essential obesity, essential thinness, thyroid thinness (hyperthyroidism) and Simmonds' disease. Estimations were made of the basal metabolic rate, respiratory quotient, specific dynamic action of several test meals, dextrose tolerance, lipid tolerance, salt and water metabolism, effect of work on the respiratory quotient and hyperglycemia and effect of insulin, epinephrine and various hormone preparations. Unfortunately no comparative values for normal controls are given, and frequently the method employed is not named. Among the data are several curious values, for instance, values for the respiratory quotient of 1.03 and 0.63. The data for specific dynamic action and the effect of various drugs are irregular.

The conclusions are that the metabolic discrepancies responsible for obesity are either secondary to neuro-endocrine disturbances or autochthonous, i. e. (in the adipose tissue). Essential obesity has a constitutional or predispositional etiology. Exogenous obesity is unusual, rather there is noted an increased avidity of the adipose tissues for deposition of fat. In general this disturbance is thought to originate in the diencephalohypophysial region. The observed alterations of metabolism are secondary to the aforementioned influences. The lipogenous tendency of Bergmann is proved. On the other hand, the author states that the chief cause of pathologic thinness is anorexia, which may be psychic, but in Simmonds' disease, exophthalmic goiter and other conditions it is secondary to a disturbance of the diencephalohypophysial region, or it may represent a vegetative neurosis.

On the basis of his studies the author recommends a low caloric-high protein (to increase the specific dynamic action) diet for the treatment of obesity. For the pathologically thin person a high carbohydrate diet, insulin and psychotherapy are indicated. The review of previous work on fat and thin patients is comprehensive, and the bibliography includes about six hundred titles.

Handbook of Orthopaedic Surgery By Alfred R. Shands Jr, M.D., Associate Professor of Surgery, in collaboration with Richard B. Raney, M.D., Instructor in Orthopaedic Surgery, Duke University School of Medicine. Price, \$5. Pp 593, with 169 illustrations. St. Louis: C. V. Mosby Company, 1937.

This is a book to delight the heart of those who are trying to learn medicine or who are struggling with the medical curriculum, for it lays out in a sensible manner a sensible course in orthopedic surgery.

In 1934 the Committee on Undergraduate Instruction in Orthopaedic Surgery of the American Orthopaedic Association called attention to the fact that in several of the leading medical schools approximately twenty-four class periods each of an hour's duration are profitably employed for undergraduate instruction in this special subject. The authors of this handbook have assembled a twenty-four chapter book. All of the chapters are of approximately the same length. In the various chapters are discussed the subjects that might go to form the skeleton for a useful teaching course in orthopedic surgery, and, what is more, the manuscript of each of these chapters received due criticism by one or more competent reviewers before it went to press.

While in a sense the volume was written by many authors, yet in reality, having been put together by one, or at the most two, authors, it has a comfortably uniform style throughout, and the story is continuous. The illustrations are clear and in large measure from the facile pen of Mr. Jack B. Wilson, whose original manner of medical illustrating is now so familiar. And last but not least, at the end of the book, in addition to a good index, there is a separate bibliography for each of the twenty-four chapters, giving references up to January 1937.

It goes without saying that this handbook will prove extremely useful. As an interested teacher, this reviewer inquires: Would it be possible in the next edition to devise some loose-leaf plan by which between new editions both text and references can be kept perpetually young and up to date?

La cianosis de los cardiacos negros de Ayerza. Su estudio semiológico, clínico y fisiopatológico. By Eduardo L. Capdehourat, M.D. Pp. 372. Buenos Aires, Argentine. Aniceto Lopez, 1934.

This monograph, consisting of eight chapters and sixteen case reports, is devoted to a broad consideration of the clinical entities in which cyanosis, pulmonary fibrosis, emphysema and failure of the right side of the heart, with or without sclerosis of the pulmonary artery, are manifested. The author gives syphilis little part in the pathogenesis of these states and blames chiefly chronic injury due to infections of the respiratory tract and noxious physical agents, such as dust and gases. It is clear that in Buenos Aires Ayerza's syndrome is considered much less an etiologic entity than a condition due to pathologic physiology. North American physicians are still puzzled over the apparently high incidence of "cor pulmonale" in South America. The especial objective of the dissertation is the presentation of data and discussions on pathologic physiology of cyanosis, and this is achieved in splendid fashion. The clinical observations and physiologic measurements, including studies of pulmonary ventilation, cardiac output and chemical constituents of the blood, comprise a valuable contribution to the medical literature.

Treatment of Diabetes Mellitus. By Elliott P. Joslin, M.D., M.A. Price, \$7. Pp. 707. Philadelphia: Lea & Febiger, 1937.

An extended comment on the book which is the vade-mecum in the literature on diabetes hardly seems necessary, particularly as this is the sixth edition of what may truly be called a standard textbook and book of reference.

The introduction of "protamine insulin necessitates the revision of this book." The data that have been studied to convince Joslin and his associates consist of reports of over twelve hundred cases in which this new insulin preparation has been administered. Joslin is enthusiastic about protamine insulin. He acknowledges that some patients experience difficulty in becoming adjusted to the new drug, but these instances are few and far between. As a matter of fact, only ten of the total number of patients had any difficulty. The ages of these patients varied from 7 to 62 years, and the reasons for the difficulties were many.

The remainder of the book adheres closely to the subject matter as presented in previous editions.

Röntgenatlas der Erkrankungen des Herzens und der Gefässe. By Dr. W. Brednow, Privatdozent for Internal Medicine and Roentgenology and Chief Physician of the University Medical Clinic, Göttingen. Price, 10.50 marks. Pp. 155, with 87 illustrations. Berlin: Urban & Schwarzenberg, 1936.

This is a textbook for cardiologists setting forth the roentgen evidence elicited in examination of the heart and blood vessels. Numerous models have been photographed to illustrate the various points brought out in the roentgenograms. The illustrations are exceptionally clear, and the halftone reproductions of both photographs and roentgenograms are beautifully made. The brief text is distributed, page by page, throughout the work, facing the illustrations. This is an excellent book and should be valuable for any physician utilizing roentgen aid in cardiovascular diseases.

Registro e interpretación de la actividad cardíaca. By Oscar Orias, M.D. Pp. 193, with 77 illustrations. Second edition. Buenos Aires, Argentine: El Ateneo, 1936.

This monograph describes clearly the possibilities for physiologic observation of cardiac and vascular phenomena by means of graphic methods, chiefly the optical manometers of Wiggers. The reviewer is greatly impressed with the perfection of the records used as illustrations.

PNEUMONIA DUE TO TYPE V PNEUMOCOCCUS

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AND

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The separation of twenty-nine new types of pneumococci from those formerly designated as group IV opened up an entirely new and promising field for investigation. It was apparent that these new types required study along the same lines that had been applied to the original three types in order to determine variations in the clinical picture, the prognosis and especially the possibility of treatment with serum. Variations in diseases due to the pneumococci of types I, II and III are well known. In the case of infection with type I pneumococci the tendency to affect young adults, the more frequent acute and typical onset, the termination by crisis and the striking response to therapy with specific serum are recognized. Infection with type II pneumococci is associated with a more protracted and more irregular course, with a high incidence of invasion of the blood stream, numerous complications, less likelihood of critical termination, a higher mortality and less impressive response to serum therapy. In the case of infection with type III pneumococci a tendency to affect aged persons, especially those who are debilitated and infirm, a relatively low incidence of bacteremia but a high mortality rate and in the presence of bacteremia a uniformly fatal outcome and finally the complete absence of any response to serum therapy are recognized.

Since the group IV pneumococci are the incitants in only about 25 per cent of the cases of pneumonia it appeared probable that each of the constituent types would occur but rarely. It was found, however, that while most of the types did occur but rarely, types V, VII, VIII and XIV occurred with much greater frequency than the others. These types became, therefore, the object of our immediate interest. In this paper we report our experience with pneumonia due to type V pneumococci. Our experience with pneumonia due to the pneumococci of types VII, VIII and XIV will be reported in subsequent studies.

This investigation was supported in part by a grant from Mr. Bernard M. Baruch.

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INCIDENCE

Published reports of the incidence of type V pneumonia are scarce Griffith found this type second in prevalence among the types into which he separated group IV, Robinson found this type, termed by him type IV E, the most common type during the winter of 1928 in Pittsburgh No other reports are available

During the past eight years (1928 to 1936) we observed one thousand, eight hundred and fifty cases of pneumococcic pneumonia Sixty-eight of these were due to the type V pneumococcus, giving an incidence of 3.5 per cent

Two features in the incidence of this disease have been impressive (1) a tendency to epidemicity, evidenced by the fact that groups of four or five patients have on several occasions been admitted to the hospital within a few days, and (2) an apparent increase in frequency Of the sixty-eight patients with type V pneumonia, twenty were seen in the four year period from 1928 to 1932, while forty-eight were seen in the following four year period, 1932 to 1936

TABLE 1—*Distribution of Sixty-Eight Cases of Type V Pneumonia by Year and Month*

	July	Aug	Sept	Oct	Nov	Dec	Jan	Feb	March	April	May	June	Total
1928 1929							1		1		2		4
1929 1930					2	1							3
1930 1931							5	1	1		1		8
1931 1932						2		1	1	1			5
1932 1933		1	1				2	4	1	1			10
1933 1934				1	1	1	1	2	1	1	1		9
1934 1935								3	5	2	2	1	13
1935-1936			1				6	4	1	4			16
Total	—	1	2	1	3	4	15	15	11	9	6	1	68

BACTERIOLOGY

The type V pneumococcus was originally designated by Avery as subgroup II A He pointed out that strains of this type were agglutinated to a considerable degree by serum of type II pneumonia, although the agglutination was often delayed and incomplete He noted, too, that type II antiserum protected to some extent against subgroup II A cultures, while antiserum for subgroup II A failed to protect against type II cultures

In 1929 Cope, Edwards and Rosenstein published their first paper reporting the separation of types among the pneumococci formerly called group IV In that paper the strain described by Avery was designated as type V It was shown that this organism when cultivated in blood broth mediums had a tendency to hemolyze red blood cells In some strains this tendency was more marked than in others, but in general it was much greater than for the other pneumococci studied

This organism, in contrast to many of the new types of pneumococci, must occur rarely if ever as a saprophyte in the mouths of normal persons. In no case in our experience was it found except in association with definite pneumonia.

ETIOLOGY

Certain factors which appeared to be predisposing were in general similar to those found in other types of pneumonia. Outstanding among these was infection of the upper respiratory tract, usually a common cold. This infection was present in thirty-four of the sixty-eight cases. There was a history of exposure in twenty, of trauma in two, of alcoholic stupor in three and of dietary deficiency in three. In three cases pneumonia was associated with pregnancy. In one case in which pneumonia developed while the patient was in the ward, definite contact infection was evident.

SEX AND AGE

Only seven of the sixty-eight patients were females, that is, 10.2 per cent of the group. No significance is attached to this, because pneumococcic pneumonia is predominantly a disease of males.

The ages of the patients were scattered fairly evenly, except in the fourth decade, in which age group belonged twenty-four of the sixty-eight patients.

CLINICAL PICTURE

Onset—In forty-six cases the onset of the disease was abrupt and was associated with sharp shaking chill, thoracic pain and cough and in thirty-eight cases with the expectoration of rusty or frankly hemorrhagic sputum.

In twenty-two cases the onset was atypical, occurring usually in the course of some infection of the upper respiratory tract, and characterized as a rule by irregular fever without chill.

Fever—The fever was usually of the plateau type, and in a high percentage of cases termination was by crisis. In thirteen of the eighteen cases in which recovery was obtained without serum treatment there was termination by crisis. In fifteen of the twenty-nine cases in which serum treatment was given the disease terminated by crisis.

The duration of fever tended to be prolonged. In only seven of the twenty-nine cases in which recovery occurred without serum was there termination of fever in less than one week, while in eleven cases it lasted one week or more, in three of these cases lasting more than ten days.

Headache—In twenty cases headache was a symptom early in the disease. Usually it was severe, in one case it was so severe that the presence of meningitis was suspected.

Vomiting—Vomiting occurred in nineteen cases. In several of these it was persistent, and in three it was associated with severe diarrhea.

Jaundice—The frequency with which jaundice occurred was striking. It was present in sixteen cases, a frequency several times that usually encountered. It seems not unlikely that this frequency is related to the hemolytic properties of the type V pneumococcus.

Bacteremia—Culture of the blood was made in every case as soon as possible and before the administration of serum. If the culture showed a positive result it was repeated every day until the result was negative. If the first culture showed a negative result, another was made only if there was a chill, a sudden sharp rise in temperature, persistent fever or some complication.

In eighteen of the sixty-eight cases culture showed positive results when the patient was admitted to the hospital. In addition, in two cases in which the result was at first negative, later there was a positive result. Bacteremia was therefore present in twenty cases, an incidence of 29 per cent. This is a higher incidence of bacteremia than for any other type of pneumonia in our experience.

Anoxemia—The presence of anoxemia was indicated by cyanosis and tachypnea and in four cases by the estimation of the oxygen saturation in the arterial blood. In five cases anoxemia was so marked that this feature dominated the clinical picture. In eleven cases there was anoxemia of moderate grade. In practically all the other cases a slight degree of cyanosis was noted at some period of the disease.

Severity—In general the severity of any type of pneumonia is directly related to the following factors: (1) bacteremia, (2) anoxemia, (3) the age of the patient and (4) his general state of health.

Using these factors we made in each case an estimation of the severity of the disease. In twelve cases we found it to be extremely severe, with overwhelming infection. In some of these cases there was profuse bacteremia, in one case there were 2,000 colonies per hundred cubic centimeters of blood and in another 1,200 colonies. There were also cases of meningitis and of acute bacterial endocarditis. In thirty-eight cases the disease was estimated to be moderately severe, and in only eighteen cases could the disease be regarded as mild.

SERUM TREATMENT

The successful use of serum therapy in pneumonia depends on the potency of the specific antiserum and its administration early in the course of the disease. From experience with serum for type I and type II pneumonia it is generally believed that the first two days com-

prise the most favorable period for administration and that with each day thereafter the result becomes less favorable

In thirty-nine of our cases serum treatment was given, and in only twelve cases was it given within the first three days. In the other cases treatment was given at a later period, in nine of these cases being given later than one week after the onset.

A comparison between the results in the cases in which serum was given and in those in which it was not given is shown in table 2.

The importance of early serum therapy is suggested by the comparison of results in cases in which treatment was given early and of those in which it was given late. In only two of the twelve cases in which treatment was given within the first three days did death occur. In only three of the twenty-five cases in which treatment was given within the first five days did death occur. When treatment was begun after the fifth day the mortality rate rose rapidly, death occurring in seven of the thirteen cases.

TABLE 2—*Mortality with Regard to Serum Treatment*

Cultures of Blood	Nonserum Treatment			Serum Treatment		
	Number of Cases	Number of Deaths	Mortality, Percentage	Number of Cases	Number of Deaths	Mortality, Percentage
Negative results	19	4	21	31	5	16
Positive results	10	7	70	8	5	62
Whole series	29	11	38	39	10	26

In presenting the results of serum treatment in so small a series of cases we are conscious of the limited value of the figures. However, it is our expectation that similar reports will soon be forthcoming from other institutions and that all these reports when pooled may constitute a group sufficiently large to be significant.

COMPLICATIONS

The most common complication was empyema, which occurred in seven cases. In only two of these cases had serum treatment been given.

Endocarditis was proved at autopsy in two cases. In a third case there was all the evidence usually regarded as sufficient for the diagnosis, but autopsy was not performed.

Suppurative bronchitis was present in three cases. Meningitis was present in two cases, and each of the following conditions was noted once: Otitis media, pleurisy with effusion, pulmonary abscess, purulent pericarditis, embolism of the subclavian artery and glomerular nephritis.

SUMMARY

Sixty-eight cases of pneumonia due to type V pneumococcus were studied. The distribution of these cases by months and years suggests an increasing frequency and a tendency to epidemicity.

The clinical course was characterized in most cases by an abrupt onset and a prolonged course, and in over half the cases there was termination with crisis. Headache, vomiting and jaundice were common symptoms. There was a high incidence of bacteremia and anoxemia. Complications were frequent.

In the cases in which serum treatment was given there was a lower mortality than in the cases in which serum treatment was not given. The difference was especially marked in those cases in which treatment was given early in the course of the disease.

The common concept that group IV pneumonia is always a mild infection is contradicted by this study.

EFFECT OF OXYGEN INJECTED SUBCUTANEOUSLY ON ANTIBODY FORMATION

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AND

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CHICAGO

In a communication by Barker and one of us (T. S.)¹ the effect of the subcutaneous administration of oxygen on experimentally induced anoxemia in dogs was discussed. The failure of the injected oxygen to alter the oxygen content or percentage of desaturation of the arterial blood and the lack of evidence of absorption of the injected oxygen indicate little therapeutic value for its use. However, favorable clinical results have frequently been reported, and the possibility that oxygen given subcutaneously may exert some indirect effect by stimulating the antibody-producing mechanism cannot be ignored, especially in view of the following report from the literature.

Lipkin, Podvalny and Grintzevic² have reported on the effect of the subcutaneous administration of oxygen on the titer of complement and natural hemolysin for sheep red blood cells in normal dogs and on agglutinin formation in the dogs after injections of typhoid vaccine. The titers of complement and natural hemolysin were determined for three dogs both before and after the subcutaneous injection of oxygen, the dogs receiving 30, 20 and 10 cc., respectively, of oxygen per kilogram. The complement titers decreased threefold within twenty-five days. The natural hemolysin titers decreased tenfold within eight days after the injection of oxygen and disappeared entirely within twenty-five days. To determine the effect of the subcutaneous administration of oxygen on the specific antibody response, five dogs were given typhoid

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1 Simpson, T., and Barker, M. H. A Study in Subcutaneous Oxygen Therapy, *Arch. Int. Med.*, to be published

2 Lipkin, J. J., Podvalny, P. B., and Grintzevic, O. The Action of Subcutaneous Oxygen on the Variation of Complement, Hemolysin, and on the Formation of Specific Antibodies, *Gior. di batteriol. e immunol.* **13** 661, 1934

vaccine in increasing amounts every day for ten days. Eight days after the last injection of antigen one dog was given 30 cc of oxygen per kilogram of body weight subcutaneously, the injections being continued daily for eight days. Two other dogs were given 30 and 20 cc, respectively, of oxygen per kilogram along with the injections of antigen, the two remaining dogs serving as controls. A fourfold increase in specific agglutinin titer was obtained in the dog receiving 20 cc of oxygen per kilogram within twenty days after the last injection of antigen and an eightfold increase within sixteen and twenty days, respectively, in the two dogs receiving 30 cc of oxygen per kilogram of body weight. The authors concluded that the subcutaneous introduction of oxygen caused a decrease in natural complement and hemolysin, while it stimulated the formation of specific antibodies. The importance of these results, if substantiated, is obvious. However, the number of animals used and the number of determinations made were few.

In order to determine the effect of the subcutaneous injection of oxygen on specific antibody response to the parenteral injection of bacterial antigen and on the complement titer, the following experiments were carried out.

METHODS

Six dogs weighing from 10 to 16 kilograms and ten rabbits weighing from 2 to 3 kilograms were given intravenous injections of a heat-killed suspension of type I and type II pneumococci containing approximately 2,000,000,000 organisms of each type per cubic centimeter. The dogs were given injections of increasing amounts of the antigen for ten successive days, each receiving a total of approximately 12.5 billion pneumococci of each type, the rabbits were given five successive daily injections, each receiving a total of approximately 6,500,000,000 pneumococci.

Five of the ten rabbits were given daily subcutaneous injections of approximately 30 cc of oxygen per kilogram of body weight, beginning on the day of the first injection of antigen and continuing throughout the course of the experiment. Three of the six dogs received similar daily subcutaneous injections of oxygen, starting the seventh day after the last injection of antigen and continuing throughout the course of the experiment. At no time was there evidence of complete absorption of the injected oxygen. A large excess was always present.

All animals were tested, both before immunization and at three day intervals after the last injection of antigen, for agglutinins and opsonins for type I and type II pneumococci. In addition, complement titrations were made for all rabbit serums.

The agglutination tests were set up, the usual serial dilution method being used to the limit of titer. Living type I and type II pneumococci, centrifugated from twenty-four hour dextrose broth cultures and resuspended in physiologic solution of sodium chloride, were used as antigens in the test. The tubes were incubated two hours at 37 C, and a reading was made after they had stood overnight in the icebox.

The opsonin content of the serums was determined by using the Jung³ modification of the Wright capillary pipet method. Normal whole blood of dogs was washed carefully four times with physiologic solution of sodium chloride, the leukocytes were counted and the blood was diluted with physiologic solution of sodium chloride to obtain a concentration of 10,000 leukocytes per cubic millimeter. Standard heat-killed suspensions of type I and type II pneumococci were employed throughout. Two volumes of standardized blood, 1 volume of bacterial suspension and 1 volume of undiluted serum were carefully mixed in a capillary pipet and incubated for thirty minutes at 37 C. For the controls, physiologic solution of sodium chloride was substituted for serum. Smears were made on clean glass slides and stained with the Wright stain. One hundred cells were counted on each slide, and the results were recorded as the percentage of cells showing phagocytosis.

Rabbit complement titers were determined as follows. To a series of tubes undiluted rabbit serum was added in amounts varying from 0.02 to 0.2 cc, increasing by steps of 0.02 cc. Sufficient physiologic solution of sodium chloride was then added to make the volume 1 cc. One-tenth cubic centimeter of hemolytic amboceptor, containing 2 units, and 1 cc of a 1 per cent suspension of sheep red blood cells were added to give a total volume of 2.1 cc. The results were read after incubation for one hour at 37 C. The titer was recorded as the least amount of serum giving complete hemolysis.

RESULTS

Agglutinins—The agglutinin response was markedly greater in rabbits into which type I and type II pneumococci had been injected than in dogs into which the same organisms had been injected. Likewise, the agglutinin titers for type I pneumococci were much greater than for type II pneumococci, in the case of rabbits the total average titer being twenty-five times as great and in the dogs six times as great (tables 1 and 2).

There was no significant difference between the total average agglutinin titers of the oxygen-treated and the control animals for type II pneumococci. In fact although there were minor differences in the separate sets of determinations between the oxygen-treated and the control group, the total average agglutinin titers of the rabbits were almost the same in the two groups, and the control group of dogs had a slightly higher average agglutinin titer. The same applied to the total average agglutinin titers for type I pneumococci of the dogs (tables 1 and 2).

The average agglutinin titers for type I pneumococci of the rabbits showed greater differences between the oxygen-treated and the control animals (table 1). The maximum titers were reached on the sixth day in the oxygen-treated rabbits, with an average of 1:1,408, and on the twelfth day in the controls, with an average titer of 1:864. By the twenty-first day the two groups gave approximately the same average

³ Jung, R. W. The importance of Leucocyte Counts in Phagocytic Tests, J. Lab. & Clin. Med. **21**: 760, 1936.

TABLE 1—*Agglutinin Titers of Rabbits and Dogs for Type I Pneumococci*

Animal No	B*	Time After Last Injection of Antigen, Days							Total Average Titer
		3	6	9	12	15	18	21	
Rabbits, oxygen treated									
1	10	320	1,280	1,280	1,280	640	640	320	
2	0	160	1,280	640	640	640	640	320	
3	0	40	640	640	640	320	320	320	
4	0	1,280	2,560	2,560	1,280	640	640	640	
5	0	640	1,280	1,280	1,280	640	320	320	
Average		488	1,408	1,280	1,024	576	512	384	810
Rabbits, controls									
6	0	160	1,280	1,280	1,280	640	320	320	
7	0	20	160	160	320	320	320	dead	
8	0	160	1,280	1,280	1,280	640	640	640	
9	0	320	1,280	1,280	1,280	640	320	320	
10	0	20	160	160	160	160	160	160	
Average		136	832	832	864	480	352	360	550
Dogs, oxygen treated									
1	0	20	80	160	160	20	80	80	
2	0	0	80	160	160	40	80	80	
3	0	20	80	320	320	80	160	80	
Average		13.3	80	213	213	46.6	106	80	107
Dogs, controls									
4	20	80	160	160	320	80	80	80	
5	0	20	40	80	320	40	160	160	
6	0	40	160	160	80	20	80	80	
Average		46.6	120	133	240	46.6	106	106	114

* In tables 1, 2, 5 and 6 B indicates before the injection of antigen

TABLE 2—*Agglutinin Titers of Rabbits and Dogs for Type II Pneumococci*

Animal No	B	Time After Last Injection of Antigen, Days							Total Average Titer
		3	6	9	12	15	18	21	
Rabbits, oxygen treated									
1	0	0	40	20	40	10	10	10	
2	0	0	80	20	20	10	0	0	
3	0	0	20	20	20	10	10	10	
4	0	160	40	40	40	40	40	20	
5	0	80	20	40	40	20	20	20	
Average		48	40	28	32	18	16	12	27.7
Rabbits, controls									
6	0	0	20	20	20	10	20	20	
7	0	0	0	20	20	40	20	dead	
8	0	0	0	40	40	20	20	20	
9	0	80	20	20	20	0	0	0	
10	0	0	40	80	160	80	40	20	
Average		16	16	36	52	30	20	15	26.4
Dogs, oxygen treated									
1	0	0	80	10	20	0	0	0	
2	0	0	80	20	20	10	0	0	
3	0	0	40	20	20	0	0	0	
Average		0	66	16	20	3	0	0	15
Dogs, controls									
4	0	0	160	40	20	20	0	0	
5	0	0	80	0	20	10	0	0	
6	0	0	40	40	40	0	0	0	
Average		0	93	26	26	10	0	0	22

titer The total average agglutinin titer of the oxygen-treated rabbits was 1 810, and that of the untreated controls was 1 550, a difference of 260 The greatest difference between the average agglutinin titers of the two groups was obtained on the sixth day, the titers for the treated rabbits averaging 576 higher than those for the controls In view, however, of the extreme variation in the agglutinin response of the individual rabbits, the significance of these differences is open to question A statistical study, with computation of the probable error and of the probability that the results were due to chance, showed that in none of the individual sets of determinations was the probability that the results were due to chance less than 1 7, which is too high to permit of these differences being called significant (table 3) The probability that the difference in the total average agglutinin titers was due to chance was 1 22, which falls in the same category

TABLE 3—*Significance of Differences in Average Agglutinin Titers for Type I Pneumococci*

	Time After Last Injection of Antigen, Days							Total Average Titer
	3	6	9	12	15	18	21	
Average titer for oxygen treated rabbits	488	1,408	1,280	1,024	576	512	384	810
Average titer for control rabbits	136	832	832	864	480	352	360	550
Difference	352	576	448	160	96	160	24	260
Probability that difference was due to chance	1 7	1 6	1 3	1 2	1 2	1 6	1 1	1 22

Opsonins—Normal dog and rabbit serums opsonized both type I and type II pneumococci Type I pneumococci were phagocytosed to the same extent in both normal dog and normal rabbit serum, averaging 43 9 per cent Normal rabbit serums averaged only 7 7 per cent, and normal dog serums averaged 27 6 per cent phagocytosis of type II pneumococci (tables 4 and 5)

The average increase in phagocytosis of pneumococci following injection of antigen of type I and type II pneumococci was approximately 10 per cent higher in dog than in rabbit serums The total average increase was about the same for both type I and type II pneumococci in dog and rabbit serums This is not at all comparable to the agglutinin response The rabbits produced higher agglutinin titers for both organisms than did the dogs, and the agglutinin titers for type I pneumococci were considerably higher than those for type II pneumococci in both dogs and rabbits

When the total average increase in percentage of phagocytosis for both type I and type II pneumococci in serums of the oxygen-treated animals is compared with that for the controls, it can readily be seen that there is no significant difference (tables 4 and 5)

TABLE 4—Percentage of Phagocytosis of Type I Pneumococci in Rabbit and Dog Serums

Animal No	B	Time After Last Injection of Antigen, Days							Total Average Phagocytosis	
		3	6	9	12	15	18	21	%	Increase, %
Rabbits, oxygen treated										
1	43	71	52	36	75	76	82	63		
2	46	71	54	74	60	58	78	78		
3	49	61	54	73	63	68	87	70		
4	46	72	83	83	66	53	64	72		
5	38	66	71	80	71	63	89	86		
Average	44.4	68.2	62.8	69.2	67	63.6	80	73.8	69.2	24.8
Rabbits, controls										
6	40	67	76	84	73	80	89	76		
7	42	55	68	52	66	84	83	dead		
8	47	68	80	71	73	73	91	66		
9	40	63	83	69	89	83	95	75		
10	42	52	57	64	69	62	72	64		
Average	42.2	61	72.8	68	74	76.4	86	70.2	72.5	30.3
Dogs, oxygen treated										
1	42	81	73	54	82	83	95	89		
3	47	81	85	82	88	89	94	87		
3	46	68	84	86	91	94	91	90		
Average	45	76.4	80.6	74	87	88.6	93.3	85.3	83.6	38.6
Dogs, controls										
4	44	80	72	67	78	90	92	90		
5	44	80	88	78	89	86	94	87		
6	45	78	91	75	78	91	92	87		
Average	44.3	79.3	83.6	73.3	81.6	89	92.6	88	83.9	39.6

TABLE 5—Percentage of Phagocytosis of Type II Pneumococci in Rabbit and Dog Serums

Animal No	B	Time After Last Injection of Antigen, Days							Total Average Phagocytosis		
		3	6	9	12	15	18	21	%	Increase, %	
Rabbits, oxygen treated											
1	9	19	57	37	31	11	23	8			
2	6	7	27	22	23	2	18	7			
3	8	14	65	58	24	16	24	12			
4	6	80	87	80	57	38	53	22			
5	9	50	76	73	62	16	23	15			
Average	7.6	34	62.4	54	39.4	16.6	29.2	12.8	35.5	27.9	
Rabbits, controls											
6	11	29	77	42	33	18	13	6			
7	7	11	11	23	30	25	16	dead			
8	10	11	72	33	43	14	29	5			
9	5	21	45	37	47	8	26	18			
10	6	2	35	65	70	33	61	55			
Average	7.8	14.8	48	40	44.6	19.6	29	21	31.0	23.2	
Dogs, oxygen treated											
1	24	63	67	51	71	73	76	60			
2	28	61	64	71	71	46	72	60			
3	23	41	77	77	66	35	70	50			
Average	25	55	69.3	66.3	69.3	51.3	72.6	56.6	62.9	37.9	
Dogs, controls											
4	32	63	59	57	79	85	79	80			
5	30	74	63	76	75	75	46	70			
6	29	71	73	51	57	48	34	49			
Average	30.3	69.3	65	61.3	70.3	69.3	53	66.3	64.9	34.6	

Complement—Complement titrations were made only for rabbit sera. There was considerable variation in the normal complement concentrations among the individual rabbits. After the injections of antigen the average amount of complement rose slightly and maintained a fairly constant level, with a few minor variations, throughout the following three weeks. The oxygen-treated rabbits showed an average of only 0.005 cc more complement than the controls, a difference that is without significance. These results are in marked contrast to those of Lipkin, Podvalny and Grintzevic,² who observed a marked decrease in complement titer for dogs given oxygen subcutaneously.

TABLE 6—*Complement Titers for Rabbits*

Rabbit No	B	Time After Last Injection of Antigen, Days							Total Average Titer	Total Average Increase
		3	6	9	12	15	18	21		
Oxygen treated										
1	0.14	0.06	0.04	0.01	0.06	0.06	0.06	0.06		
2	0.02	0.08	0.08	0.18	0.10	0.10	0.12	0.10		
3	0.12	0.06	0.00	0.16	0.08	0.10	0.08	0.10		
4	0.06	0.06	0.06	0.18	0.10	0.06	0.06	0.06		
5	0.14	0.06	0.08	0.18	0.10	0.08	0.08	0.10		
Average	0.116	0.064	0.052	0.16	0.088	0.08	0.08	0.084	0.084	0.029
Controls										
6	0.14	0.04	0.04	0.14	0.04	0.06	0.08	0.08		
7	0.14	0.02	0.04	0.18	0.14	0.16	0.18	dead		
8	0.12	0.06	0.04	0.10	0.04	0.06	0.06	0.08		
9	0.10	0.06	0.06	0.10	0.08	0.06	0.10	0.08		
10	0.06	0.08	0.08	0.10	0.04	0.08	0.10	0.10		
Average	0.112	0.072	0.072	0.124	0.088	0.084	0.104	0.085	0.089	0.023

COMMENT

The lack of any observable effect of the subcutaneous injection of oxygen on the production of agglutinin and opsonin in rabbits and dogs and on the complement titers of rabbits might be considered surprising, in view of the marked effect reported by Lipkin, Podvalny and Grintzevic.² However, a critical examination of their data reveals that, owing to the small number of animals employed and the few determinations made, the possibility that their results were due to random sampling was great. This possibility is brought out clearly in our work if the extreme variation in formation of antibodies by the individual animals is observed. This is especially pronounced in the agglutinin titers of rabbits for type I pneumococci (table 1). By comparing only the rabbit in the oxygen-treated group producing the highest titer with the control rabbit producing the lowest titer, the effect of treatment with oxygen would have been to increase the agglutinin content eightfold. Conversely, it would be possible by appropriate selection to obtain a control rabbit with a titer four times as high as that of an oxygen-treated rabbit. The results

show that with relatively large groups of treated and control animals these discrepancies in individual response are minimized. Furthermore, statistical examination is a valuable aid in determining the true significance of observed differences.

From a physiologic point of view this lack of effect is not surprising, especially in view of the recent work¹ showing the lack of utilization by the anoxemic dog of oxygen injected subcutaneously. Even if an excess of oxygen could affect the antibody-producing mechanism, this lack of utilization would preclude its reaching the site of antibody formation and hence its exciting any effect. Furthermore, it is difficult to understand why as slight an amount of oxygen as would be obtained by the subcutaneous route, even if it were all absorbed, would stimulate antibody formation when oxygen is normally absorbed in far greater quantities by way of the respiratory tract.

SUMMARY

A study was made of the effect of the subcutaneous administration of oxygen on the production of agglutinin and opsonin in rabbits and dogs into which heat-killed type I and type II pneumococci had been injected and on the complement titers of rabbits.

Into ten rabbits and six dogs were injected heat-killed pneumococci of type I and type II. Half were given daily subcutaneous injections of 30 cc of oxygen per kilogram of body weight, the remainder being used as controls. Determinations of the opsonin and agglutinin contents of the serums were made for all the animals at frequent intervals over a period of three weeks after the last injection of antigen. Complement titrations were made at the same time for all rabbit serums.

The subcutaneous administration of oxygen had no effect on the opsonin content of the serums of the dogs or rabbits for either type I or type II pneumococci.

The subcutaneous administration of oxygen had no effect on the agglutinin titers of dog serums for type I and type II pneumococci nor had it any effect on the agglutinin titers of rabbit serums for type II pneumococci.

An apparent effect of the subcutaneous injection of oxygen on the agglutinin titers of rabbits for type I pneumococci was found statistically to be without significance.

CLASSIFICATION AND TERMINOLOGY OF LEUKEMIA AND ALLIED DISORDERS

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Hughes Bennett¹ proposed the term leukocythemia and Virchow² the term *Leukämie* almost simultaneously in 1845 to designate the disease which is now regarded almost uniformly by English speaking physicians as leukemia. Later two types were differentiated and called splenomyelogenous leukemia and lymphatic leukemia. Reschad and Schilling-Torgau,³ in 1913, described a third common type, monocytic leukemia. A number of other types of leukemia or related disorders are reported on frequently in the medical literature, among these being chloroleukemia, leukosarcoma, plasma cell leukemia, eosinophilic leukemia, basophilic leukemia, megakaryocytic leukemia, leukanemia, pseudoleukemia, aleukemic leukemia and others to be mentioned later.

There has been a tendency in recent years to substitute the terms leukosis, myelosis and lymphadenosis for leukemia, myelogenous leukemia and lymphogenous leukemia, respectively. The reasons presented for the substitution of these newer terms for the older equivalents are that the newer terms are said to indicate more fundamental hematopoietic changes. It is well to bear in mind, however, that the term leukemia is well defined in much the same manner as is the term anemia. Obviously both are incorrect if one wishes to translate them literally. Perhaps in the future, with advancement of knowledge, a more precise designation may be possible, but in the present state of inadequate knowledge it appears both unwise and unnecessary to adopt new terms or additional equivalent terms to describe pathologic states already well described by a terminology which has existed for many decades.

Because of these and other complicating factors students and physicians frequently are confused concerning the classification and terminology.

From the Department of Medicine of the Peiping Union Medical College

1 Bennett, J H. Case of Hypertrophy of the Spleen and Liver, in Which Death Took Place from Suppuration of the Blood, *Edinburgh M & S J* **64** 413, 1845

2 Virchow, R. Weisses Blut, *Notiz a d Geb d Nat - u Heilk* **33** 151, 1845

3 Reschad, H, and Schilling-Torgau, V. Ueber eine neue Leukämie durch echte Uebergangsformen (Splenozystenleukämie) und ihre Bedeutung für die Selbständigkeit dieser Zellen, *München med Wchnschr* **60** 1981, 1913

nology of leukemia That the disease or diseases in all variations may be designated by a simple terminology and classified in a rational and uniform manner is shown in the following paragraphs

Leukemia, in general, is classified on the basis of whether it is acute or chronic, leukemic or subleukemic (aleukemic) It is common practice to combine with these clinical terms the anatomic name of the strain of cells which plays the dominant rôle in the leukemic process Thus one may speak of acute lymphocytic leukemia, chronic monocytic leukemia and other types Some workers prefer to indicate the origin of the cells which are concerned and to designate the types as myelogenous (myeloid or medullary) leukemia or lymphogenous (lymphoid or lymphatic) leukemia Still other workers choose to make use of the conventional nomenclature for neoplastic diseases and designate the types of leukemia by such terms as leukemic lymphoblastoma, leukemic myeloblastoma or leukemic monoblastoma (table 1)

All variations and combinations of the aforementioned terms are in common use, but rarely does one find that an author is consistent in adhering to any one of the systems mentioned Thus, many workers speak of myelogenous and lymphatic leukemia, whereas it would be more proper to speak of myelogenous and lymphogenous leukemia I can find no justification for the use of the term lymphatic to designate the type of leukemia in which lymphocytic cells are the chief elements concerned Furthermore, there is no comparable term to designate leukemia arising from the cells of the bone marrow Neither does there seem to be any reason for using the terms myeloid and lymphoid when myelogenous and lymphogenous are meant

Myelogenous leukemia obviously is a general term indicating that the cells of the leukemic process arise from the bone marrow Therefore it should be applicable to the types of leukemia in which basophilic, eosinophilic, neutrophilic and megakaryocytic leukocytes, respectively, or their precursors are concerned This, however, is not the usual practice The term myelogenous leukemia is used commonly to designate that type of leukemia in which neutrophilic leukocytes and their precursors are the cells involved This usage has been carried over from the early workers, who were not aware that myelogenous leukemia of other types occurred Some physicians have substituted the term myelocytic leukemia This also is undesirable, since myelocytes of different types occur and the designation is not specific

In order to clarify and simplify the classification of leukemia, it is suggested that some such plan as that outlined in the accompanying table (table 2) be followed According to this plan the disease commonly referred to as chronic myelogenous leukemia would be more specifically designated as chronic neutrophilocytic leukemia This

term would be comparable to chronic lymphocytic or chronic monocytic leukemia. If less specific designation is made necessary or is desirable, one may speak properly of chronic myelogenous or chronic lymphogenous leukemia.

TABLE 1—*Classification of Leukemia and New Growths of the Hematopoietic System Based on the Conventional Nomenclature for Neoplasms*

Normal Cells in Hematopoietic Organs	Conventional Nomenclature of Neoplasms Applied to Cells of Hematopoietic Organs	Types of Leukemia and of Some Other Diseases Classified Under the Name of the Tumor
Polymorphonuclear leukocytes and their precursors—myelocytes and myeloblasts	Myeloblastoma	1 Myelosarcoma 2 Chloroleukemia or chloroleukosarcoma or chloroma 3 Neutrophilic, basophilic or eosinophilic leukemia 4 Myeloblastic leukemia
Lymphocytes and lymphoblasts	Lymphoblastoma	1 Lymphosarcoma 2 Leukosarcoma 3 Lymphocytic leukemia 4 Lymphoblastic leukemia 5 ? Lymphogranuloma (Hodgkin's disease) 6 ? Small round cell sarcoma 7 ? Mycosis fungoides
Monocytes and monoblasts	Monoblastoma	1 Monosarcoma 2 Monocytic leukemia
Megakaryocytes and megakaryoblasts	Megakaryoblastoma	1 Megakaryocytic leukemia 2 Megakaryoblastic leukemia 3 ? Lymphogranuloma (Hodgkin's disease)
Plasma cells	Plasmoma or plasmacytoma	1 Plasma cell myeloma 2 Plasma cell leukemia 3 Plasmacytoma
Erythrocytes and their precursors—reticulocytes, normoblasts, erythroblasts and megaloblasts	Erythroblastoma	1 Erythrosarcoma 2 ? Erythroblastic anemia 3 ? Erythremia (polycythaemia vera)
Mesenchyme cells (primitive fibroblasts, primitive connective tissue cells, reticular cells of the reticular syncytium)	Reticuloma or reticular cytoma	1 Reticulum cell sarcoma 2 Stem cell (hemohistioblastic or embryonal cell or lymphoid cytoid) leukemia
Macrophages (histiocytes, clasmacocytes, reticuloendothelial cells)	Histioblastoma or reticuloendothelioma	1 Histioblastoma or reticuloendothelioma 2 Xanthoma (diseases of Gaucher, Niemann Pick and Christian)
Endothelial cells of common blood and lymph vessels	Endothelioma	1 Hemangioendothelioma 2 Lymphangioendothelioma 3 ? Perithelioma
Fibrocytes and fibroblasts	Fibroblastoma	1 Fibrosarcoma

* Modified from Forkner, C. E. Leukemia, in Nelson Loose Leaf Living Medicine, New York, Thomas Nelson & Sons, 1937, vol. 4

TERMINOLOGY OF MONOCYTIC LEUKEMIA

The origin of the monocyte is still controversial. Some workers believe that monocytes arise from myeloblasts in the bone marrow, others, that they are derived from lymphoid cells, and still others, that they develop from primitive mesenchyme cells, from fibroblasts or from

TABLE 2—*Classification of Leukemia (Leucemia, Leukosis, Leucocythemia)*

Clinical Designation	General Type of Leukemia	Cell of Origin	Specific Type of Leukemia†	Synonyms Depending on Common Usage, on Course of Disease or on Clinical or Hematologic Characteristics
Leukemia or subleukemic (aleukemic) leukemia (acute or chronic)	Myelogenous (arising from cells of bone marrow)	Myeloblast	NEUTROPHILOCYTIC LEUKEMIA	Myelogenous, myeloid, myelocytic or myeloblastic leukemia, myelosis
			Eosinophilocytic leukemia	Eosinophilic leukemia
			Basophilocytic leukemia	Basophilic leukemia
			Chloroleukemia	Chloroma or chloroleukosarcoma
Lymphogenous (arising from cells of lymphoid tissue)	Lymphoblast	Myeloblast and megakaryoblast	Erythroleukemia	Leukemia associated with erythremia
		Megakaryoblast	Megakaryocytic leukemia	
			LYMPHOCYTIC LEUKEMIA	Lymphogenous, lymphoid, lymphatic or lymphoblastic leukemia, lymphoblastoma leukaemicum, lymphadenosis
Lymphogenous or myelogenous	Primitive mesenchymal cell		Leukosarcoma	Lymphosarcoma associated with leukemia
			Stem cell leukemia	Hemohistioblastic, embryonal or lymphoidocytic leukemia
		Plasma cell, myeloblast and lymphoblast	Plasma cell leukemia	Plasmacytoma with leukemia or multiple myeloma with leukemia
Disputed	Monoblast		MONOCYTIC LEUKEMIA	Histiocytic leukemia, reticulosis, reticulo endotheliosis reticulum cell leukemia, reticulosarcoma

* Modified from Forkner, O. E. Leukemia, in Nelson Loose Leaf Living Medicine, New York, Thomas Nelson & Sons, 1937, vol. 4

† The common types are given in capital letters

macrophages. Hence one cannot speak of monocytic leukemia in terms of the origin of the type cell.

Some workers, particularly Naegeli,⁴ Piney,⁵ Anagnostu,⁶ Kracke and Garver⁷ and others, owing to the fact that they have regarded the monocyte as a derivative of the myeloblast, have not accepted monocytic leukemia as a distinct disease entity but have regarded it as a transitory phase in myelogenous leukemia. Reich⁸ and Fontana⁹ have presented patients with conditions believed to be due to monocytic leukemia, but the conditions subsequently were said to be considered as having been transformed into myelogenous leukemia. The evidence for this apparent transformation was that at first the blood contained predominatingly cells resembling monocytes, but as the terminal stage approached the predominating cells resembled myeloblasts. Farrar and Cameron¹⁰ have discussed this question. Obviously the blast cells of each of the various kinds of leukocytes are difficult to differentiate. It is only by the use of all available methods that definite conclusions may be reached. The evidence seems insufficient to justify the acceptance of a transformation of one type of leukemia into another.

Space does not permit a detailed discussion of the origin and independence of the monocyte. This has been the subject of much controversy during the past twenty years. I¹¹ reviewed the problem on two occasions, and more recently Doan and Wiseman¹² published

4 Naegeli, O. *Blutkrankheiten und Blutdiagnostik*, ed. 4, Berlin, Julius Springer, 1923.

5 Piney, A. *Recent Advances in Hematology*, London, J. & A. Churchill, 1928.

6 Anagnostu, J. Ueber einen seltenen Fall von chronischer monozytoider Promyelozyten-Leukämie, *Folia haemat* **43** 446, 1931.

7 Kracke, R. R., and Garver, H. Differential Diagnosis of the Leukemic States, with Particular Reference to the Immature Cell Types, *J. A. M. A.* **104** 697 (March 2) 1935.

8 Reich, C. Case of Monocytoid Myeloblastic Leukemia, *New York State J. Med.* **32** 1193 (Oct. 15) 1932.

9 Fontana, A. A proposito della leucemia monocitica, *Minerva med.* **2** 673 (Nov. 17) 1932.

10 Farrar, G. E., Jr., and Cameron, J. D. Monocytic Leukemia with Data on the Individuality and Development of the Monocyte, *Am. J. M. Sc.* **184** 763, 1932.

11 Forkner, C. E. (a) Material from Lymph Nodes. IV. The Heterology of Lymphoid Tissue with Special Reference to the Monocyte, *Supravital Studies, J. Exper. Med.* **49** 323, 1929, (b) The Origin of Monocytes in Certain Lymph Nodes and Their Genetic Relation to Other Connective Tissue Cells, *ibid.* **52** 385, 1930.

12 Doan, C. A., and Wiseman, B. K. The Monocyte, Monocytosis and Monocytic Leukosis, *Ann. Int. Med.* **8** 383, 1934.

their views. Let it suffice to say that relatively recent studies, particularly those of Sabin and her associates, have given overwhelming evidence to support the theory of the existence of monocytes as an independent strain of cells. I¹³ have presented clinical, hematologic and histologic evidence which indicates that acute monocytic leukemia usually is characterized by a syndrome which differs from that of other forms of acute leukemia.

Still another source of confusion is in the terminology relating to monocytes. They have been designated by some workers as transitional cells, large mononuclear leukocytes, blood histiocytes or endothelial leukocytes. Some authors have failed to appreciate the distinction between the so-called blood histiocytes and the hemohistioblasts of Ferrata. Hence, several papers refer to cases of hemohistioblastic leukemia, although it is obvious from the text that monocytic leukemia is meant. Osgood and Lyght¹⁴ apparently used stem cell leukemia and monocytic leukemia as synonymous terms. Dameshek¹⁵ has confused the issue by indicating that monoblasts, hemohistioblasts, clasmatocytes, reticular cells, histiocytes and resting wandering cells are identical, an opinion which is entirely without support. Furthermore, Dameshek has stated, quite incorrectly, that the consensus is that the monocyte is derived directly from the histiocyte and has given as evidence that vital staining and supravital staining methods support this view. On the contrary, the brilliant researches of Evans and Scott,¹⁶ of Simpson,¹⁷ of Sabin and her associates¹⁸ and of others using these technics have resulted in a strict separation of these two groups of cells. These misleading errors in terminology have been pointed out by Clough¹⁹ and by Levine²⁰.

13 Forkner, C. E. Clinical and Pathologic Differentiation of the Acute Leukemias, *Arch. Int. Med.* **53** 1 (Jan.) 1934.

14 Osgood, C. W., and Lyght, C. E. Monocytic Leukemia, *J. Lab. & Clin. Med.* **18** 612, 1933.

15 Dameshek, W. Acute Monocytic (Histiocytic) Leukemia, *Arch. Int. Med.* **46** 718 (Oct.) 1930.

16 Evans, H. M., and Scott, K. J. On the Differential Reaction to Vital Dyes Exhibited by the Two Great Groups of Connective Tissue Cells, *Contrib. Embryol.* **10** 1, 1921.

17 Simpson, M. E. The Experimental Production of Macrophages in the Circulating Blood, *J. M. Research* **43** 77, 1922.

18 Sabin, F. R., Doan, C. A., and Cunningham, R. S. Discrimination of Two Types of Phagocytic Cells in the Connective Tissues by the Supravital Technique, *Contrib. Embryol.* **16** 125, 1925.

19 Clough, P. W. Monocytic Leukemia, *Bull. Johns Hopkins Hosp.* **51** 148, 1932.

20 Levine, V. Monocytic Leukemia. Report of Nine Cases, *Folia haemat.* **52** 305, 1934.

A number of authors have used the terms reticulosis and reticulo-endotheliosis as synonyms for monocytic leukemia. The term aleukemic reticulosis was used by Letterer²¹ to designate a condition in which there was general systemic hyperplasia of the endothelium of the blood vessels of the hematopoietic organs but no leukemic blood picture. Ewald²² observed a case of acute leukemia, probably monocytic in type, which he labeled leukemic reticulo-endotheliosis. Griffin and Watkins²³ discussed cases of so called subleukemic splenic reticulo-endotheliosis. Bohne and Huismans²⁴ and Dameshek²⁵ have reviewed the subject of reticulosis and aleukemic reticulosis. Dameshek found thirteen acceptable reports of cases of aleukemic reticulosis in the literature and suggested that the condition is a distinct entity related to monocytic leukemia in the same way that subleukemic lymphogenous leukemia and subleukemic myelogenous leukemia are related respectively to lymphogenous leukemia and myelogenous leukemia. Dameshek's patient had recurrent bouts of fever and progressive weakness which terminated after six months in death. On physical examination at first nothing abnormal was noted. Later a lymph node in the neck became slightly enlarged, and subsequently the spleen became palpable. During observation there occurred fever of the typical Pel-Ebstein type. Anemia, thrombopenia and leukopenia were marked, but there were normal proportions of the various blood cells. Biopsy of the bone marrow and postmortem observations revealed a proliferation of reticulo-endothelial cells in the lymph nodes, spleen, bone marrow, liver and other organs. Reticulin fibers were demonstrated easily in the pathologic tissues. Giant cells of the Steinberg-Reed type were numerous. Rare eosinophils were present.

I can find no reason for regarding these conditions as due to reticulo-endothelioses, unless one wishes to change the whole nomenclature of the diseases ordinarily regarded as lymphoblastomas. Dameshek has not made it clear whether he regarded the disease as a lesion of the cells of the reticular syncytium or as a lesion of those cells commonly called macrophages (histiocytes or clasmatocytes) which are differentiated toward more definite types with a function of

21 Letterer, E. Aleukamische Retikulose, *Frankfurt Ztschr f Path* **30** 377, 1924.

22 Ewald, O. Die leukamische Reticuloendotheliose, *Deutsches Arch f klin Med* **142** 222, 1923.

23 Griffin, H. Z., and Watkins, C. H. Distinction Between Splenic Anemia and Subleukemic Splenic Reticulo-Endotheliosis, *Am J M Sc* **188** 761, 1934.

24 Bohne, C., and Huismans, L. Beitrage zur Kenntnis der chronischen leukamischen Reticuloendotheliosen, *Virchows Arch f path Anat* **283** 575, 1932.

25 Dameshek, W. Proliferative Diseases of the Reticulo-Endothelial System II. Aleukemic Reticulosis, *Folia haemat* **49** 64, 1933.

phagocytosis No adequate reason was given for not classifying the condition as lymphoblastoma of the Hodgkin type, as was done by Krumbhaar²⁶ in a similar case In certain instances in which the lesions are not so typical of Hodgkin's disease the condition may be more appropriately termed reticulum cell sarcoma If the cells do indeed meet the description of those of the monocyte series, then monoblastoma would be an appropriate term

The terms aleukemic and leukemic reticulosis have been used to designate monocytic leukemia because some authors believe in the theory that monocytes have their origin from the reticulo-endothelial system These terms have been used repeatedly by a considerable number of writers, notwithstanding the fact that there exists no clear-cut evidence to indicate that monocytes are related in any intimate way with the reticulo-endothelial system considered in its strict sense I^{11b} have demonstrated that monocytes do not react specifically to the agents used for demonstrating the reticulo-endothelial system and that they therefore must be considered as independent of the system

From the histologic point of view it appears to be as proper to regard lymphocytic or neutrophilic leukemia or any other type of leukemia as an example of reticulo-endotheliosis, although to do so is meaningless Hodgkin's disease, Kaposi's disease, Gaucher's disease and hyperplasia of the macrophages in the blood-forming organs as the result of infection have been designated by various workers as reticulosis or reticulo-endotheliosis of one or another sort The terms reticulosis and reticulo-endotheliosis as synonyms for monocytic leukemia add nothing but confusion to the subject and cannot be acceptable to the large group of workers who do not accept the view that monocytes arise from macrophages (reticulo-endothelial cells)

Krahn²⁷ and Akiba²⁸ said that they believed that the conditions called leukemic and subleukemic reticulo-endotheliosis are not true leukemia but the result of general systemic infection

TERMINOLOGY OF SUBLEUKEMIC (ALEUKEMIC) LEUKEMIA, PSEUDO-LEUKEMIA, LEUKANEMIA AND RELATED STATES

Leukemia is a disease which exhibits manifold characteristics both clinically and histologically It may be shown eventually that the con-

26 Krumbhaar, E B Hodgkin's Disease of Bone Marrow and Spleen Without Apparent Involvement of Lymph Nodes, *Am J M Sc* **182** 764, 1931

27 Krahn, H Reticuloendotheliale Reaktion oder "Reticuloendotheliose," *Deutsches Arch f klin Med* **152** 179, 1926

28 Akiba, R Ueber Wucherung der Retikulo-Endothelien in Milz- und Lymphknoten und ihre Beziehung zu den leukamischen Erkrankungen, *Virchows Arch f path Anat* **260** 262, 1926

ditions which today are regarded as various types of leukemia are a heterogeneous group of diseases. It is well established that in some cases of leukemia there is no significant change in the total number of leukocytes in the blood throughout the course of the disease, and in other cases there may be leukopenia throughout and that in many cases at different periods in the disease there is a characteristic decreased, normal or increased number of cells, whereas in the majority of cases there is a marked increase in the total number of leukocytes in the blood throughout the course of the illness. Furthermore, it is established, almost without exception if careful qualitative studies of the blood are made, that immature leukocytes, often in significant numbers, are demonstrable in the blood and that there is a disproportion in the kinds of leukocytes, even though there may be a decrease or no increase in their total number in the blood.

The physician not thoroughly familiar with the field of hematology will find the group of diseases included in this subgroup most confusing. Obviously there is much need for a simplified concept of these processes based on a fundamental principle, so as not to allow the subject to be confused by an endless combination of terms proposed by those who report cases. Although the use of the expression aleukemic leukemia implies that there are no immature cells in the blood but that leukemia is present as demonstrated by other means, this has not been the usual interpretation of the process. Frequently the term has been used interchangeably and synonymously with pseudoleukemia, and it is therefore open to the same criticism. A variety of clinical conditions have been called aleukemic leukemia. Chief among this group are leukemic states in which there is either temporary or persistent failure of the proliferating immature cells to enter into or to remain in the blood stream. Many workers have objected to the term aleukemic leukemia on the basis that it is a contradiction of terms. It seems appropriate to avoid this contradiction by the substitution of the term subleukemic leukemia.

Is it possible to formulate any organized concept of the disease states variously referred to as pseudoleukemia, anemia pseudoleukaemica, pseudoleukanemia, splenic pseudoleukemia, aleukemic leukemia, aleukemic leukosis, aleukemic lymphatic leukemia, aleukemic myelogenous leukemia, aleukemic lymphadenosis, aleukemic myelosis, aleukemic reticulosis, aleukemic reticulo-endotheliosis, aleukemia, aleukia, aleukemic erythroblastosis, aleukocythemic leukemia, medullary leukemia, aplastic leukemia, anemoleukemia, leukanemia, subleukemic leukemia, leukopenic leukemia or lymphoblastoma aleukaemicum? This is not a mere list of names that have been invented but a list of terms which have been used by various physicians. Furthermore, I have not listed all, merely some of those terms which have been employed repeatedly. All com-

binations of these terms have been used by various writers, each basing his classification or terminology on some clinical, histologic or other characteristic of the disease studied. As previously stated, it is logical and practicable to divide all the instances of leukemia with regard to acute and chronic forms and further with regard to leukemic and sub-leukemic varieties (table 2), the latter term indicating whether or not an increased number of leukocytes is present in the blood. Further separation is made depending on the type of cell involved in the leukemic process. Thus a simple classification is evolved which encompasses all the types of leukemia encountered and is devoid of the heterogeneous terms which add confusion. For the sake of clearness some of the commonly used terms will be discussed, mostly for the purpose of indicating their shortcomings and of orienting the reader of the medical literature on the subject.

Soon after Virchow² described lymphocytic leukemia, Cohnheim²⁹ recorded a case in which the tissue presented identical anatomic characteristics but the blood did not show an increase in the proportion of white and red corpuscles. He proposed the term pseudoleukemia to designate this picture. It should be remembered that the study of Cohnheim was made prior to the use of apparatus for the direct enumeration of blood cells and prior to the development of methods giving clear differentiation of the ages and types of leukocytes. Since the publication of this original work the term pseudoleukemia has been applied, often indiscriminately, to a large variety of conditions, including subleukemic lymphogenous or myelogenous leukemia, lymphosarcoma, lymphogranuloma (Hodgkin's disease), xanthoma (Schuller-Christian's disease), Niemann-Pick's disease, Gaucher's disease, enlargement of the lymph nodes associated with infections and various other obscure diseases having certain characteristics suggesting leukemia.

Ebstein³⁰ described cases of acute pseudoleukemia, and Pinkus³¹ observed that in the pseudoleukemia of Cohnheim there was a relative increase in the number of lymphocytes in the blood, often with the presence of immature cells.

The term pseudoleukemia is an unfortunate one, in that it has been used not only to include cases like those of Cohnheim, Pinkus and others but more or less as a scrap basket for various atypical pictures.

29 Cohnheim. Ein Fall von Pseudoleukämie, Virchows Arch f path Anat **33** 451, 1865

30 Ebstein, W. Ueber die akute Leukämie und Pseudoleukämie, Deutsches Arch f klin Med **44** 343, 1888-1889

31 Pinkus, F., in Nothnagel, C. Spezielle Pathologie und Therapie, Vienna, A. Holder, 1901, vol. 8, pt. 1, cited by Ewing, J. Neoplastic Diseases ed. 3 Philadelphia, W. B. Saunders Company, 1928

simulating, in one way or another, leukemia Naegeli,³² for example, under the heading pseudoleukemia included the following subheads

A Lymphocytomas

- 1 Aleukemic lymphadenosis (true pseudoleukemia)
- 2 Lymphosarcomatosis (Kundrat)
- 3 Localized lymphosarcoma

B Myelosis

- 1 Aleukemic myelosis

C Granulomas

- 1 Lymphogranuloma (Paltauf)
- 2 Tuberculous granuloma
- 3 Syphilitic granuloma
- 4 Leprous granuloma

D Splenic pseudoleukemia, with isolated enlarged spleen

E Myelogenous pseudoleukemia (myeloma)

Obviously it is no longer possible to speak of pseudoleukemia in any strict sense of the word, and the term is becoming unpopular in hematologic literature

Von Jaksch³³ described the blood picture that is sometimes seen in anemic infants and with which his name has been associated (von Jaksch's anemia, anemia pseudoleukaemica infantum, secondary infective myelemia of infancy, rachitic myelemia, splenic anemia of infancy or pseudoleukaemia infectiva) The young child usually has a large spleen, severe chronic anemia, a low color index, leukocytosis and a variable number of immature leukocytes, megaloblasts and normoblasts in the blood Infection and undernutrition are the most common causes of this syndrome It is undoubted, however, that a number of different clinical entities have in the past been included under this heading Among these, in addition to infection and undernutrition, may be mentioned erythroblastic anemia, hemolytic jaundice, subleukemic leukemia and Banti's syndrome The term von Jaksch's anemia and its various equivalents have, for the most part, been discarded in favor of more precise expressions

Since Hirschfeld³⁴ pointed out the existence of subleukemic myelogenous leukemia (aleukemic myelosis) a large number of cases

32 Naegeli, O Blutkrankheiten und Blutdiagnostik, ed 5, Berlin, Julius Springer, 1931

33 von Jaksch, R Ueber Leukämie und Leukocytose im Kindesalter, Wien klin Wchnschr 2 435, 1889

34 Hirschfeld, H Die generalisierte aleukämische Myelose und ihre Stellung im System der leukämischen Erkrankungen, Ztschr f klin Med 80 126, 1914

have been reported, and there has been a tendency to create a clinical entity Jaffé³⁵ reviewed the subject but proposed to restrict the term to those conditions in which there is no leukocytosis and in which no immature cells are encountered at any time in the blood Under these conditions subleukemic myelogenous leukemia would be an exceedingly rare disease, and the diagnosis would rest almost entirely with the pathologist Such restriction seems hardly justifiable on the basis of existing knowledge Most writers have designated myelogenous leukemia, either acute or chronic, in which there is no increase in the total leukocytes of the blood as aleukemic or subleukemic myelogenous leukemia In many of the cases reported there have been varying numbers of myelocytes and myeloblasts in the blood In some of these cases large numbers of nucleated red blood corpuscles have been present in the blood, and extensive erythropoiesis has been observed in the tissues In every respect, except for the blood picture, subleukemic myelogenous leukemia may be identical with the leukemic form of the disease Cases of acute involvement in which there is no qualitative or little quantitative change in the leukocytes may be confused easily with cases of thrombocytopenic purpura haemorrhagica or with aplastic anemia, whereas in the analogous cases of chronic involvement the clinical picture is similar to that of early Banti's syndrome Stephens and Bredeck³⁶ discussed the relation of aleukemic myelosis to osteosclerosis Baldrige and Fowler³⁷ reported on ten cases and discussed at length the clinical features of the disease

Subleukemic lymphogenous leukemia (aleukemic lymphogenous leukemia or aleukemic lymphadenosis) is a disease state in which there is lymphogenous leukemia without an increase in the leukocyte count, although there may be any degree of alteration qualitatively in the leukocytes The term aleukemic as a modifier of the term leukemia has invited the inclusion of a host of diseases into this category In many of the cases reported there was only a superficial resemblance to leukemia Subleukemic lymphogenous leukemia should include only those conditions in which the diagnosis of leukemia is established and in which the total leukocyte count is not significantly elevated Obviously in many of the cases there will eventually be shown a frank leukemic blood picture No essential difference histologically has been shown to exist in the tissues in subleukemic lymphogenous leukemia and frank leukemic lymphogenous leukemia Theories relative to the reasons why

35 Jaffé, R H Aleukemic Myelosis, Arch Path **3** 56 (Jan) 1927

36 Stephens, D J, and Bredeck, J F Aleukemic Myelosis with Osteosclerosis, Ann Int Med **6** 1087, 1933

37 Baldrige, C W, and Fowler, W M Aleukemic Myelosis, Arch Int Med **52** 852 (Dec) 1933

some conditions remain subleukemic and others are frankly leukemic have been discussed elsewhere³⁸ In the literature there is no clear distinction between conditions regarded by some authors as subleukemic (aleukemic) lymphogenous leukemia and by others as pseudoleukemia of the lymphogenous type

A number of papers have been written in recent years referring to cases of so-called aplastic leukemia or to cases of leukemia in which the clinical picture has simulated closely that of aplastic anemia Abt³⁹ and Baar⁴⁰ pointed out the frequency with which subleukemic leukemia in children is confused with aplastic anemia, the latter disease being much the rarer of the two Akerrén⁴¹ recorded the case of a 4 year old boy who had pain in the region of the hip joint, pallor, emaciation and weakness Three months after the onset he showed profound anemia with leukopenia, lymphocytes predominating, and thrombopenia There was no enlargement of lymph nodes, spleen or liver until five months after the onset Hemorrhagic phenomena appeared, and the child died seven months after the appearance of the first symptoms Postmortem examination showed typical lymphogenous leukemia It was pointed out in the discussion that in some cases of leukemia in childhood the onset is characterized by more or less marked anemia of the aplastic type, without an increase in the number of abnormal types of lymphocytes and without enlargement of the liver, spleen or lymph nodes Livingstone⁴² and Weber⁴³ each studied an adult in whom the condition closely simulated aplastic anemia, but at autopsy it proved to be subleukemic lymphogenous leukemia (aleukemic lymphadenosis) in the first and subleukemic myelogenous leukemia (aleukemic myelosis) in the second case Weber and Weisswange⁴⁴ studied a similar case in a boy of 11 years At the beginning of the illness the picture simulated that of aplastic anemia Autopsy demonstrated lymphocytic infiltration, especially of the kidneys, liver, testes, bone marrow and

38 Forkner, C E Leukemia and Allied Disorders, to be published

39 Abt, I A Case of Aleukemic Leukemia with Clinical Symptoms of Plastic Anemia, *M Clin North America* **8** 427, 1924

40 Baar, H Ueber akute aleukozytämische Leukämie im Kindesalter, *Jahrb f Kinderh* **54** 1, 1924

41 Akerren, Y Zur Diagnose und Differentialdiagnose der Lymphadenose, besonders im Kindesalter, *Acta pædiat* **13** 501, 1932

42 Livingstone, J L Lymphatic Leukemia Simulating Aplastic Anaemia, *Proc Roy Soc Med* **25** 1400, 1932

43 Weber, F P Aleukemic Myelosis of the Leucopenic Type, Clinically Simulating Chronic Aplastic Anemia, *Quart J Med* **1** 409, 1932

44 Weber, F P, and Weisswange, W Lymphadenosis Commencing with the Clinical Picture of Hypoplastic Anaemia, *Proc Roy Soc Med* **26** 1012, 1933, *Aplastische Anämie und Leukämie*, *Deutsches Arch f klin Med* **176** 422, 1934

lymph nodes Zypkin⁴⁵ said he believed that aplastic anemia may be present in the terminal stage of leukemia, and Mallory⁴⁶ referred to a case of leukemia, proved at biopsy of the bone marrow, in which autopsy revealed a totally aplastic marrow

Von Leube⁴⁷ described a rapidly progressive disorder characterized by changes in the blood which suggested pernicious anemia combined with myelogenous leukemia Severe anemia, a high color index and the presence of excessive numbers of nucleated red corpuscles and of large immature leukocytes in the blood were noted The author said he believed that this syndrome, which was called leukanemia, is an independent disease not included in the same category with either pernicious anemia or leukemia

Drysdale⁴⁸ and Symmers⁴⁹ reviewed the earlier literature and reported additional cases Symmers gave as his conclusion that leukanemia is characterized clinically by an extremely rapid course and by changes in the blood, bone marrow, spleen, liver and lymph nodes that partake of the nature of both pernicious anemia and myelogenous leukemia He said he considered leukanemia not as an independent disease but as one of a group of rapidly progressive derangements of the blood-forming tissues due to infection

Pinkerton⁵⁰ described a case of acute aleukemic erythroblastosis which may be regarded as a case of leukanemia Muller and Werthemann⁵¹ rightly pointed out that the term leukanemia is purely descriptive and should not be regarded as indicating a distinct entity They noted that the signs referred to as characteristic of leukanemia have been observed in cases of acute myelogenous leukemia, nitrobenzene poisoning, pernicious anemia, anemia following roentgen irradiation, lymphosarcomatosis, malaria, sepsis and metastatic carcinoma involving bone marrow

45 Zypkin, S M Ueber aplastische Leukanemie, Virchows Arch f path Anat **258** 600, 1925

46 Lymphoblastoma, ? Giant Follicular Type, with Involvement of Spleen, Kidney, Bone Marrow and Lymph Glands, Cabot Case 21281, New England J Med **213** 67 (July 11) 1935

47 von Leube, W Rapid verlaufende schwere Anämie mit gleichzeitiger leukämischer Veränderung des Blutbildes, Berl klin Wchnschr **37** 851, 1900

48 Drysdale, J H Leukanaemia Its Relation to Leukaemia and Pernicious Anemia, Quart, J Med **1** 89, 1907-1908

49 Symmers, D Leukanemia, J A M A **76** 156 (Jan 15) 1921

50 Pinkerton, H Aleukemic Leukemia and Atypical Leukemoid Conditions Report of Seven Cases Including One of Acute Erythroblastosis, Arch Path **7** 567 (April) 1929

51 Muller, A, and Werthemann, A Unter dem Bilde der sog Leukanemie verlaufende Karzinose des Knochenmarkes bei kleinem, verstecktem Mammakarzinom, Folia haemat **46** 429, 1932

That in myelogenous leukemia at times, particularly immediately subsequent to treatment, there may be a large number of nucleated red corpuscles in the blood is within the experience of all who have observed any significant number of cases. Beiglböck⁵² and many others have reported cases of this type and have discussed the relation of the picture to the syndrome of leukanemia.

SUMMARY AND CONCLUSIONS

The confusion existing in the classification and terminology of diseases of the blood-forming organs, particularly of leukemia and related disorders, is reviewed and discussed.

A classification (table 2) is presented which encompasses all known variants of leukemia and which simplifies the concepts of these disorders.

⁵² Beiglböck, W. Subleukämische Myelose mit dem klinischen Bild einer perniziösen Anämie (Ein Beitrag zur Frage der sogenannten Leukanämie), *Wien klin Wchnschr* **47** 962 (Aug 3) 1934.

SHOCK SYNDROME IN THERAPEUTIC HYPERPYREXIA

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Studies of severe reactions in hyperpyrexia are highly suggestive of shock, and it is the thesis of this paper that the severe reactions are actually true shock. Although there have been numerous investigations into the theory of shock, no one theory has been adduced that is satisfactory to all workers in this field. Recent studies, however, have stressed the importance of a diminished volume of blood and an increased vascular permeability in the production of the shock syndrome¹. In fact, Moon^{1b} has defined shock as "the disparity between the volume of blood and the volume-capacity of the vascular system". He has stated that shock may result either from loss of blood or fluid or from atony or dilatation of the vascular walls, especially of the capillaries and venules, combinations of these two factors being the rule. According to this concept, increased capillary permeability, with leakage of plasma through the vascular walls, occurs as a result of stasis and anoxemia, still further diminishing the volume of blood.

A workable division of the types of shock or acute failure of the circulation into five groups has been offered by Blalock^{1a}.

- 1 The hematogenic type—brought on by hemorrhage or rapid severe dehydration (burns, muscle and intestinal trauma) resulting in a diminution of blood volume and an increase of capillary permeability

From the Boston Psychopathic Hospital

1 (a) Blalock, A. Acute Circulatory Failure as Exemplified by Shock and Hemorrhage, *Surg, Gynec & Obst* **58** 551 (March) 1934. (b) Moon, V. H. Shock Syndrome in Medicine and Surgery, *Ann Int Med* **8** 1633 (June) 1935. (c) Mann, F. C., and Essex, H. E. Present Status of the Problem of Traumatic Shock, *Am J Surg* **28** 160 (April) 1935. (d) Harrison, T. R. Failure of the Circulation, Baltimore, Williams & Wilkins Company, 1935, pp 17-27.

- 2 The neurogenic type—brought on by stimuli acting through the nervous system (spinal anesthesia, a blow in the solar plexus, a bullet shot) resulting in vasodilation, an increase in capillary permeability and then a diminution of blood volume
- 3 The vasogenic type—vascular dilation brought on by agents acting directly on the vascular walls (histamine, anaphylactic shock) leading to increased vascular permeability and hemoconcentration
- 4 The cardiogenic type—occurring in conditions in which there is sudden and widespread damage of the cardiac muscle (coronary thrombosis, acute diphtheritic myocarditis, prolonged tachycardia) (venous distention occurs in this group)
- 5 Unclassified types—the mechanism not being clear, possibly involving several factors (postoperative shock, severe acute infections, acute surgical emergencies, ether anesthesia)

Shock with peripheral vascular failure occurs in many conditions in addition to those just mentioned, such as intestinal obstruction, acute adrenal insufficiency, cholera, diabetic coma, poisoning and fatal exposure to cold² The clinical picture of heat prostration is suggestive of the shock syndrome^{2a} In many conditions of shock there is not only a loss of fluid, with a reduction in the blood volume, but a loss of considerable salt from the body (intestinal obstruction, diabetic coma, acute adrenal insufficiency and other conditions³) The pathologic picture is the same in many of these conditions and is typical of the shock syndrome^{1b}

Experience in this clinic has shown that in therapeutic hyperpyrexia induced by hot moist air, as in the Kettering hypertherm, a clinical picture of shock is occasionally seen at temperatures of about 106 F or above An opportunity has thus been afforded to make clinical and laboratory observations on patients reacting in this manner to hyperpyrexia

STUDY

Methods of Induction of Fever—Fever is induced by means of the Kettering hypertherm The patient, during fasting, lies in an insulated cabinet and is exposed to a current of hot moist air of a fixed velocity and with a humidity of from 35 to 50 per cent The level of the dry bulb temperature ranges from 155 to 160 F, the level of the wet bulb temperature from 130 to 135 F The body of the patient is first bathed with liquid petrolatum and then covered with terry cloth towels to prevent cutaneous burns The head protrudes from the cabinet and is cooled with an electric fan The body temperature is raised to levels of 104 and 106 F

2 (a) Atchley, D W Role of Peripheral Circulatory Failure in Clinical Medicine, New England J Med **213** 861 (Oct 31) 1935 (b) Harkins, H N Shock Due to Freezing Shift of Body Fluids and Associated Blood Concentration Changes, Proc Soc Exper Biol & Med **32** 432 (Dec) 1934 (c) Blalock^{1a} Moon^{1b} Mann and Essex^{1c} Harrison^{1d}

3 Moon^{1b} Atchley^{2a}

(rectal), depending on the condition treated, these levels being reached usually in from sixty to ninety minutes. The current of hot moist air is then turned off, and the patient is covered with woolen blankets to prolong the increased body temperature as long as desired, usually for from three to five hours. Six-tenths per cent saline solution is given by mouth as desired, and an attempt is made to reach an intake of from 1,000 to 1,200 cc during the first ninety minutes, the total intake being about 3 or 4 liters during a five hour prolongation of temperature. Treatment is given once a week.

Subjects—Artificial fever therapy has been given to patients with ages ranging from 6 to 60 years. The contraindications to this type of treatment are few and include marked hypertension, active pulmonary tuberculosis, acute nephritis, marked debility and myocardial failure. There are persons, however, who though in good physical condition cannot be given artificial fever by means of the hypertherm because of an inability to tolerate the high wet and dry bulb temperatures of the environmental blanket of air. It is in these persons especially that severe reactions are most likely to occur.

RESULTS

Shock Reactions—Severe reactions, considered as shock, occurred in eight patients with ages ranging from 19 to 56 years, and death resulted in two of this group.

An analysis of the data, as given in the accompanying table, reveals that the reactions occurred at temperatures of 106 F or above, the body temperature usually showing some further rise during the reaction. In all patients an attempt was being made to prolong the body temperature at a level close to 106 F, in five patients (M F, M L, S M, J P and D T) by shutting off the air current and covering the body with woolen blankets and in three patients (G G, P M and A Y) by continuous exposure to the current of hot moist air.

The impending shock was ushered in by a sudden increase in the pulse rate, pallor or cyanosis of the skin, a continued or rapid rise in the body temperature, fluttering of the eyelids, twitchings of muscles of the face or extremities, vomiting or sudden quietness, suggesting coma in a patient who had previously complained bitterly of the heat.

Readings of the blood pressure when obtained at this time showed low levels (68 systolic and 48 diastolic, 60 systolic and 54 diastolic, 60 systolic and 30 diastolic), and in three patients the radial pulse was either weak or absent. The pulse rate at the onset was usually rapid, from 120 to 164 per minute, and in one patient (S M) it increased from 130 to 180.

In six patients these initial symptoms were followed by clonic or tonic convulsive movements of the jaw, extremities or trunk, and in five of the latter group the rigidity, either localized or generalized, was so marked that it was difficult to differentiate it from the tonic state of a convulsive seizure or muscle rigors due to heat cramps⁴. In one patient

4 Talbott, J H. Heat Cramps, *Medicine* 14 323 (Sept) 1935

Patient, Age and Sex	Treat- ment No	Diagnosis	Temperature, Pulse Rate and Blood Pressure		Time of Reaction	Intake of Fluids (0.6% Sahne Solution), Cc		Vomiting	Diarrhea
			At Start of Treatment	At Time of Reaction					
M F 19 F	2	Juvenile dementia paralytica, rheumatic heart disease, mitral stenosis	98.2 132 106/70	106.0 164 Pulse weak	1 3/4 hr after onset of treatment, current off 1 1/2 hr after start of treatment at tempera- ture of 105.6 F and pulse rate of 144, temperature prolonged for 15 min at 105.6 to 106 F	First hr 800 Second hr 400 Total 1,200		Large amounts total of more than 1 L at onset of reaction	Some at onset of reaction
A Y 33 F	5	Dementia paralytica	99.0 100 100/60	106.0 132	2 hr and 20 min after start of treatment, current on during entire period temper- ature prolonged for 1 hr at 106 to 107 F	First hr 600 Second hr 600 Total 1,200		15 min before onset of reaction, projec- tile, also during reaction, large amounts, as much at 1 L at one time	
S M 36 M	9	Dementia paralytica	98.4 76 120/80	106.8 rose to 107.4 130 rose to 180 60/54	1 1/2 hr after start of treatment current off 1 1/4 hr after the start of treatment at tempera- ture of 106.8 F and pulse rate of 146, tem- perature prolonged for 15 min at 106.8 F	First hr 600 Second hr 200 Total 800		After onset of reaction, foul vomitus for next 48 hr	24 hr after reactions, foul diarrhea per- sisting for 48 hr
J P 40 M	1	Acute gonorrheal urethritis	98.4 51 100/60	107.8 142	2 3/4 hr after start of treatment current off 2 hr after start of treatment at tempera- ture of 107 F and pulse rate of 140 tem- perature rose to 107.8 F in 45 min	First hr 300 Second hr 800 Third hr 200 Total 1,300		Large amount of dark brown ma- terial, 1 hr after onset of reaction some vomiting 5 hr after onset	Some diarrhea 1 hr after onset of reaction
M L 45 M	6	Primary atrophy of optic nerve	98.2 76 140/90	107.4 156 68/48	1 3/4 hr after start of treatment current off 1 1/4 hr after start of treatment at tempera- ture of 105.4 F and pulse rate of 132 temperature rose to 107.4 F in 1/2 hr	First hr 1,000 Second hr 400 Total 1,400		Considerable vomiting 1 hr after onset of reaction	Foul, occurred about 1 hr after onset of reaction
G G 49 M	1	Tabes dorsalis, atrophy of optic nerve	98.6 78	106.2 160 Pulse very weak pressure not ob- tainable	1 1/2 hr after start of treatment current on during entire period temperature prolonged for 1/2 hr from 106 to 106.4 F pulse rate rose from 118 to 160	First hr 200 Second hr 0 Total 200		1 1/2 hr after reac- tion vomitus dark brown, with fecal odor	Occurred 1 1/2 hr after onset of reaction and until death stool "reddish"
P M 51 M	10	Dementia paralytica	98.4 76 108/78	106.6 120 Pulse weak	2 hr after start of treatment current on during entire period temperature prolonged for 1/2 hr at 106 to 106.6 F	First hr 400 Second hr 100 Total 500		Large amount, con- sisting of most of fluids taken, 1/2 hr before onset of reaction	Occurred 24 hr after onset of reaction foul persisted for 48 hr
D T 56 F	5	Dementia paralytica, diabetes mellitus chronic bronchitis	98.6 90 130/70	106.7 rose to 107 155 60/30	1 1/4 hr after start of treatment current off 1 hr after onset of treatment at tempera- ture of 106 F and pulse rate of 142 temperature prolonged for 1/4 hr from 106 to 106.6 F	First hr 800 Second hr 0 Total 800		5 hr after onset of reaction vom- ited large amount of dark brown material with foul odor	Occurred 5 hr after start of reaction foul

Tremors, Twitchings, Convulsions	Delirium and Coma	Excitement	Cough	Drugs	Course and Treatment	Other Data
Twitchings of muscles of face, feet and hands, fluttering of eyelids followed by generalized convulsion	Delirium	Considerable jactitation			Intravenous infusion of 600 cc of 0.9% saline and 5% dextrose solution, convulsions ceased after infusion, patient well after 1 hr	
Quivering of eyelids and twitchings of muscles of upper extremities at onset of reaction, reflexes increased	Delirium	Hyperactive		Sodium amytal, 3 grains at start of treatment	Calcium gluconate intramuscularly gave no relief for muscle tremors, fluids by mouth caused vomiting, intravenous infusion impossible because of poor condition of veins, hypodermoclysis of 2,000 cc of 0.9% saline and 3% dextrose solution, patient recovered in 1 3/4 hr	
Fluttering of lids, twitchings of facial muscles, involuntary movements of fingers 1 1/2 hr after onset of reaction, followed by repeated generalized convulsions for 4 hr, loss of control of vesical and rectal sphincters	Coma	Maniacal, considerable jactitation			Intravenous infusion of 750 cc and then 500 cc of 0.9% saline and 4% dextrose solution, caffeine with sodium benzoate subcutaneously, ether, 4 cc, intramuscularly, soluble phenobarbital U S P (sodium phenobarbital) in repeated doses, 22 grains intramuscularly for convulsions, stormy convalescence of 8 wk	Subnormal temperature for 3 days, marked icterus, pyuria, with very high nonprotein nitrogen content, thrombophlebitis of thighs, broncho pneumonia, sepsis, polyneuritis, severe anemia
Clonic movements of jaw and extremities at start followed by rigidity of extremities and trunk and spasms of abdominal muscles, loss of control of vesical and rectal sphincters	Delirium	Considerable jactitation, made worse by application of ice to skin		Sodium amytal, 3 grains, 3/4 hr after start of treatment	Intravenous infusions of 0.9% saline and 5 and 10% dextrose solution, three bromides N F, 30 grains (2 Gm), by rectum for excitement, recovered in 24 hr	Respirations during reaction irregular and slow, with apnea and hyperpnea
Clonic movements of left hand 1 hr after onset of reaction, loss of control of rectal sphincter	Delirium followed by coma	Maniacal and very hyperactive			Intravenous infusion of 650 cc of 0.9% saline and 8% dextrose solution, recovered in 24 hr	Very restless during treatment, during reaction respirations slow, shallow, irregular, with periods of apnea
Generalized rigidity 1 1/2 hr after onset of reaction, muscle rigidity or generalized convulsion 3/4 hr before this loss of control of vesical and rectal sphincters	Coma	Marked restlessness and hyperactivity	Considerable thick tenacious sputum and frothy mucopurulent material	Sodium amytal, 6 grains, 1/4 hr before treatment	Artificial respiration for failure of respiration, 5% carbon dioxide and oxygen, with some improvement epinephrine and caffeine subcutaneously, calcium gluconate did not relieve convulsion hypodermoclyses of 1,500 cc of 0.9% saline and 2 1/2% dextrose solution 8 and 10 hr after reaction, morphine, 1/4 grain, subcutaneously 1 hr before death	At time of reaction skin pale, no cyanosis, respiration slow, shallow, irregular, with long apneic periods, restlessness, lungs revealed many râles, death due to respiratory failure
Twitchings and clonic movements of jaw muscles at onset of reaction, occasional rigidity of extremities, Chvostek + knee and ankle jerks not increased	Delirium followed by coma	Considerable hyperactivity	Cough productive of thick tenacious mucopurulent material	Sodium amytal, 3 grains, 1 1/2 hr after start of treatment	Intravenous infusion of 1,000 cc of 0.9% saline and 3% dextrose solution, recovered in 2 1/2 hr, except for weakness and diarrhea, which persisted for 48 hr	
Generalized rigidity 2 hr after onset of reaction, repeated convulsions, clonic movements of left upper extremity, paralysis of left side of face, left upper and lower extremities and right lower extremity, loss of control of vesical and rectal sphincters	Coma	Hyperactive, some jactitation		Morphine, 1/4 grain, subcutaneously 1/4 hr after start of treatment	Intravenous infusion of 0.9% saline and 10% dextrose solution, 2,400 cc in 3 hr, epinephrine intravenously, 5% carbon dioxide and oxygen, blood pressure rose to 135/60 5 hr after reaction death due to respiratory paralysis	Urine contained no acetone, sugar or diacetic acid, breathing labored, nail beds cyanotic, auricular fibrillation during reaction, basal pulmonary râles, autopsy

(S M) repeated tonic and clonic convulsive seizures occurred over a period of four hours and resembled closely those due to strychnine poisoning and tetanus, the seizures being initiated by the slightest stimulus, such as a flash of light, a touch on the body, a jarring of the bed or the closing of a door, and being accompanied with maniacal excitement (A similar response has been observed in patients with heat cramps, for whom a cool breeze or a sudden jarring of the bed was sufficient to throw the affected muscles into contraction ⁴) In another patient (D T) convulsions recurred infrequently up to the time of death In a third patient (J P) spasmodic movements of the abdominal muscles occurred

The intake of 0.6 per cent saline solution up to the time of the onset of the reaction ranged from 200 to 1,400 cc, 200 to 1,000 cc during the first hour and 0 to 800 cc during the second hour The need of a sufficient intake of fluid is increased by the vomiting and diarrhea which also occur Vomiting occurred in all our patients before, during or after the onset of the reaction, and in some cases was considerable, an amount practically equal to the intake of fluid during the fever treatment being disgorged The vomitus was usually foul, that of one patient (G G) had a fecal odor, and that of three patients was dark brown Diarrhea, usually accompanied with a foul odor, was a prominent symptom in seven patients, occurring during the reaction and even over a period of forty-eight hours The stool of one patient (G G) was reported as "reddish" In four patients loss of control of the bladder and in five patients loss of control of the rectal sphincter occurred

In all patients considerable hyperactivity, jactitation and maniacal excitement occurred, and it was necessary to restrain them This episode was either preceded or followed by coma or delirium or both

In three patients (P M, G G and D T) clinical signs of pulmonary edema were present In the first two there was considerable coughing, productive of thick mucopurulent and tenacious sputum In the third patient aspiration of the trachea was performed because of gurgling râles and was productive of bloody mucus, the diagnosis of pulmonary edema being verified on postmortem examination

The skin of each patient was hot and dry This is important, since severe reactions on exposure to a high temperature, as in heat stroke, are most likely to occur when sweating ceases ⁵

Drugs were administered to five patients of this group before or during fever therapy to three patients, 3 grains (0.2 Gm) of sodium amytal, to one patient, 6 grains (0.4 Gm) of sodium amytal, and to the fifth patient, $\frac{1}{6}$ grain (10 mg) of morphine sulfate subcutaneously

⁵ Hill, L The Nature, Prevention, and Treatment of Heat Hyperpyrexia The Physiological Aspect, Brit M J 1 397 (March 20) 1920

Six patients survived the treatment, five recovering completely in from one to forty-eight hours, with no residual findings or complaints. The sixth patient (S M) experienced a stormy convalescence of eight weeks, and since the course in this case and in two others (G G, D T) in which death occurred are of interest, detailed protocols will be given.

REPORTS OF CASES

CASE 1—S M, a 42 year old man suffering from dementia paralytica, had had treatment for approximately five years consisting of three malarial paroxysms, nine periods of fever due to typhoid vaccine, twenty diathermy treatments and fifty-nine injections of tryparsamide intravenously. After temporary improvement he relapsed mentally and according to the serologic evidence. Fever was then induced by means of the Kettering hypertherm.

Physical examination of the patient indicated a lesion at the apex of the left lung, and roentgenograms corroborated this finding. Examination of the urine showed 5 leukocytes and a rare erythrocyte per high power field. Except for the neurologic signs of dementia paralytica, the examination showed no further abnormality.

One fever treatment by means of the electric blanket and eight treatments in the hypertherm over a period of eight weeks were well tolerated. The ninth fever treatment with the hypertherm was given on July 8, 1935, and although given under the same circumstances as the previous ones, led to shock. The protocol of this treatment is given in detail.

- | | |
|-----------|---|
| 9 15 a m | Pulse rate, 84, temperature, 98.4 F, blood pressure, 120 systolic and 80 diastolic, patient placed in hypertherm |
| 10 15 a m | Pulse rate, 120, temperature 106.6 F, current turned off, patient covered with woolen blankets, total intake of fluid, 600 cc of 0.6 per cent saline solution |
| 10 30 a m | Pulse rate, 146, temperature, 106.8 F |
| 10 45 a m | Pulse rate, 150, temperature, 107.2 F, marked pallor of face, weak pulse, patient uncovered, skin rubbed with ice, fans directed at body, total intake of fluid, 800 cc of 0.6 per cent saline solution |
| 11 00 a m | Stuporous, pulse rate, 180, temperature, 107.4 F |
| 11 20 a m | Pulse rate, 180, temperature, 107.4 F |
| 11 53 a m | Pulse rate, 180, temperature, 107.4 F, blood pressure, 60 systolic and 54 diastolic, caffeine with sodium benzoate, 7½ grains (0.5 Gm), subcutaneously, intravenous infusion of 750 cc of 0.9 per cent saline and 4 per cent dextrose solution started, sample of blood taken after injection of 75 cc of fluids showed value for plasma chloride of 546 mg per hundred cubic centimeters |
| 12 00 m | Blood pressure, 65 systolic |
| 12 10 p m | Pulse rate, 106, temperature, 106.2 F, blood pressure, 75 systolic and 60 diastolic, twitchings of muscles of body and fingers and about mouth, fluttering of eyelids, wide dilatation of pupils |
| 12 18 p m | Blood pressure, 75 systolic and 60 diastolic, rapid, repeated, violent attacks of clonic movements of arms and legs and shrieking, marked hyperactivity, patient restrained, touching patient, flash of light, jar of bed or application of ice to body caused violent clonic movements, clisis terminated |

- 12 30 p m Convulsions continued, pulse rate, 164, temperature, 104 F
- 1 00 p m Convulsions continued, pulse rate, 156, temperature, 103 F
- 1 00 to 2 35 p m Soluble phenobarbital U S P (sodium phenobarbital), 16 grains (1 Gm) and ether, 4 cc, intramuscularly, convulsions continued
- 1 55 p m Pulse rate, 176, temperature, 107 F
- 3 00 p m Pulse rate, 120, temperature, 103.6 F, respiratory rate, 40, convulsions continued but less violent, 500 cc of 5 per cent solution of dextrose intravenously followed by profuse perspiration, patient semicomatose
- 8 00 p m Pulse rate, 128, temperature, 102.8 F, respiratory rate, 36, 1,600 cc of 5 per cent dextrose and 0.9 per cent saline solution subcutaneously
- 10 00 p m Pulse rate, 120, temperature, 104.2 F, respiratory rate, 26, blood pressure, 78 systolic and 68 diastolic, caffeine, 7½ grains (0.5 Gm), subcutaneously
- 12 00 m Pulse rate, 120, temperature, 103.8 F, respiratory rate, 26, blood pressure, 78 systolic and 68 diastolic, caffeine repeated
- 2 00 a m Pulse rate, 140

The blood pressure remained low for twenty-four hours after the shock reaction (84 systolic and 68 diastolic). In addition, the patient had diarrhea, with foul stools. Two days after the reaction the patient was unable to retain any food by mouth, and the rectal temperature was subnormal (96 to 96.8 F). On the third day a subicteric tint of the conjunctivae was noticed, and the patient was drowsy, apathetic and confused. Examination of the urine showed a slight trace of albumin, 20 leukocytes and many clumps of pus cells per high power field. His memory was impaired, and bilateral ankle clonus, the Gordon reflex and no abdominal reflex on the left were noted. Neurologic and mental changes had occurred as a result of the shock reaction. Because of the vomiting of food and fluids, hypodermoclyses of saline and dextrose solution were given.

The jaundice became more marked and persisted for eight days (July 11 to 19), the icteric index rising to 85. The van den Bergh test showed a delayed indirect reaction. Examination of the urine revealed no bile, slight traces of albumin and pus cells. The nonprotein nitrogen value rose to 88 mg per hundred cubic centimeters of blood. The white cell count was as high as 26,600, the red cell count, 3,940,000, and the hemoglobin content, 90 per cent (Tallqvist). During this period cellulitis and phlebitis of both thighs occurred, possibly owing to the clyses. This was followed by bronchopneumonia and pitting edema of the ankles, legs, abdomen and sacrum. The patient's condition was poor. He was irritable and restless and took little food. Repeated catheterizations were necessary because of incontinence and distention of the bladder.

From July 20 to 31 the nonprotein nitrogen content of the blood ranged from 73 to 137 mg, the urine continued to show albumin and pus cells and the specific gravity ranged from 1.008 to 1.010. General anasarca was present. The blood pressure was 130 systolic and 60 diastolic. The heart was normal. The pulse rate varied from 100 to 115, and the temperature was normal. Irrigations of the bladder with potassium permanganate were given. Otitis media developed on the left side.

From August 1 to 15 the nonprotein nitrogen content of the blood ranged from 96 to 135 mg. A large abscess of the back developed over the upper pole of each kidney, and a decubitus developed. The anemia became more marked, the red cell count being 2,680,000, the hemoglobin value 55 per cent (Sahli) and the white cell count as high as 25,580. The blood smear revealed 86 per cent polymorphonuclear leukocytes. A Mosenthal function test of the kidneys showed fixation of the specific gravity ranging from 1.005 to 1.008, the night urine amounting to 1,850 cc. Tests showed a creatinine content of the blood of 4.95 mg., and a uric acid content of 6.1 mg. A phenolsulfonphthalein function test of the kidneys showed a total output of 27 per cent in two hours. The urine continued to show albumin and pus cells. Bilateral wrist drop developed. In view of the findings the patient was placed on a high vitamin and high caloric diet and was given iron and ammonium citrates in large doses by mouth. Improvement with this therapy was rapid and marked. The abscesses over the back healed. Within two weeks the nonprotein nitrogen content fell to 38 mg., although the urine still showed pus cells. An abscessed area which developed in the right groin was incised, and the serosanguineous material obtained was cultured and examined but with negative results. Eight weeks after the reaction the patient was sufficiently improved to be discharged. He has maintained a good mental, physical and serologic improvement.

CASE 2—G. G., a 51 year old man, had had symptoms of tabes dorsalis for seven years. He had had a small amount of intravenous and intramuscular treatment, with no apparent benefit. On admission to the hospital he was having lancinating pains, difficulty in walking and in voiding urine and constipation. He had lost 20 pounds (9.1 Kg.). Aside from the signs of tabes dorsalis and atrophy of the optic nerve, his physical condition was good. The heart appeared normal, the pulse rate was 80 per minute and the blood pressure was 132 systolic and 88 diastolic. Several months previously he had received nine treatments with diathermy fever. On May 18, 1935, he was given his first fever treatment in the Kettering hypertherm, and this was accompanied with the shock phenomenon.

- 8 45 a m Pulse rate, 76, temperature, 98.6 F, patient given sodium amytal, 6 grains (0.4 Gm.), placed in hypertherm
- 9 45 a m Pulse rate, 118, temperature, 106 F, patient complained bitterly of heat throughout treatment
- 9 45 to 10 20 a m Body temperature maintained at level of 106 to 106.4 F, hypertherm current remaining on, pulse rate rose from 118 to 148 in ten minutes and then to 160, intake of fluid, only 200 cc., as patient refused to drink
- 10 20 a m Pulse rate, 160, temperature, 106.4 F, patient in coma, suddenly ceased complaining of heat, labored respirations, no pulse obtained at wrist, patient immediately removed from cabinet, fans directed at body, body surface sprayed with lukewarm water to hasten fall in temperature
- 10 30 a m Breathing ceased suddenly, artificial respiration started immediately, epinephrine, 8 minims (0.5 cc.), administered intravenously, pulse felt at wrist, color appeared good, caffeine with sodium benzoate, 3 grains (0.2 Gm.), given intravenously and 7½ grains (0.5 Gm.) subcutaneously, artificial respiration continued, since omission caused respirations to become more and more shallow, with cessation occurring soon
- 11 00 a m Applications of ice to skin

- 11 40 a m Body temperature falling, patient coughing and raising thick tenacious mucopurulent sputum, caffeine with sodium benzoate, $7\frac{1}{2}$ grains (0.5 Gm), subcutaneously
- 11 45 a m Patient rigid, muscles of arms and legs in spasm, followed by clonic movements and cyanosis of arms, difficult to make out whether convulsive seizures or localized muscle rigors, inhalations of 5 per cent carbon dioxide and oxygen given for respiratory difficulty, with relief, respirations becoming deeper, more frequent and regular, good color of lips, ears and nails, but muscle rigidity continued
- 12 00 m No increase in reflexes, no Chvostek sign, in view of position of thumbs and fingers, tetany considered, calcium gluconate, 15 grains (0.97 Gm), given intravenously, no relief of rigidity
- 12 10 p m Rigidity continued, patient still in coma, stertorous breathing, restlessness, rectal incontinence, loose watery stools
- 2 30 p m Temperature, 101.4 F, pulse rate, 140, of fair quality
- 3 30 p m Temperature, 101 F, pulse rate, 95
- 4 00 p m Temperature, 101.4 F, pulse rate, 98, respiratory rate, 22, coma continued, paleness of skin and nail beds, coughing continued, productive of thick, tenacious, mucopurulent sputum, breath, foul, tongue, dry, only feeble first apical sound heard, blood pressure not obtainable, coarse basal râles over both lungs, no distention of abdomen, no edema of extremities, no biceps, triceps, wrist, patellar or abdominal reflexes, no Babinski sign, vesical and rectal incontinence
- 5 30 p m Caffeine with sodium benzoate, $7\frac{1}{2}$ grains (0.5 Gm), subcutaneously, vomiting of dark brown fluid with fecal odor, thin watery bowel movements, coma continued, stertorous breathing, thick tenacious sputum
- 7 00 p m Pulse rate, 108, respirations, 28, 1,500 cc of 2.5 per cent dextrose and 0.9 per cent saline solution subcutaneously, patient awakened from stupor, complained of cold, hot water bottles and blankets applied, vomiting, coughing, rectal and vesical incontinence, reddish brown stools
- 8 20 p m Temperature, 103.6 F, pulse rate, 114, respiratory rate, 30, clysis terminated, vomiting of dark brown, watery material, repeated watery dejecta
- 9 00 p m Complaints of pains in chest and costovertebral regions, restlessness, wanted something to put him to sleep, some fluid retained by mouth
- 9 30 p m Pulse rate, 90, respiratory rate, 40, dozing, pulse weak, respirations shallow
- 10 00 p m Pulse rate, 92, respiratory rate, 40, blood pressure not obtainable by auscultation, perspiration and restlessness
- 10 15 p m Pulse rate, 90, respiratory rate, 40, complaints of shortness of breath, dozing
- 11 05 p m Pulse rate, 90, respiratory rate, 40, poor color, perspiring, pulse of poor quality, caffeine, $7\frac{1}{2}$ grains (0.5 Gm), subcutaneously
- 11 25 p m Morphine, $\frac{1}{8}$ grain (8 mg), subcutaneously for restlessness

- 11 35 p m 1,500 cc of 0.9 per cent saline and 2.5 per cent dextrose solution subcutaneously
- 11 55 p m Poor color, pulse rate, 90 and weak, respiratory rate, 42 and shallow
- 12 00 m Digifoline, 3 grains (0.2 Gm), subcutaneously, pulse rate, 88 (?)
- 12 14 a m Pulseless
- 12 18 a m Epinephrine, 15 minims (1 cc), subcutaneously
- 12 20 a m Respirations ceased, at no time during shock reaction was blood pressure obtainable

The outstanding observations in this case were vascular collapse, coma, convulsions, loss of sphincteric control, pulmonary edema, respiratory paralysis and neurologic changes as a result of the shock reaction. The respiratory distress was considerably relieved by inhalations of 5 per cent carbon dioxide and oxygen. Death was probably hastened by the injudicious use of morphine 1 hour before. Permission for a postmortem examination was not obtained.

CASE 3—D T, a 56 year old woman, was admitted with a diagnosis of dementia paralytica,⁶ diabetes mellitus and chronic bronchitis. Mental deterioration had been noticed for two months. The blood showed a positive Kahn reaction. Examination of the spinal fluid revealed a positive Wassermann reaction, 160 lymphocytes per cubic millimeter, a total protein content of 78 mg per hundred cubic centimeters, a positive Pandy reaction and a colloidal gold reaction of 5555543210.

Examination of the patient revealed that she weighed 148 pounds (67 Kg). The lungs were normal. The heart was not enlarged to percussion, and the sounds were of fair quality. A short harsh systolic murmur was noted at the apex and was not transmitted. The rhythm was regular. The aortic second sound was greater than the pulmonic second sound. The rate was 72. The blood pressure was 114 systolic and 68 diastolic. A scar (gallbladder operation) was noted over the upper right portion of the rectus muscle, and another scar (operation on the urinary bladder) was noted in the lower midabdominal region. The liver was felt in the right midclavicular line 2 fingerbreadths below the costal margin. The edge was smooth and thickened but not tender. The pupils were small and of an Argyll Robertson type. The knee jerks were absent, but the ankle jerks were present.

The value for blood sugar during fasting was 200 mg. The patient was receiving a diabetic diet containing 125 Gm of carbohydrate, 50 Gm of protein and 50 Gm of fat, with 10, 10 and 5 units of insulin daily. A roentgenogram of the chest showed evidence of chronic bronchitis that was not noted on physical examination. The patient received four fever treatments at weekly intervals without alarming symptoms, although she complained of discomfort more than the average patient. For this reason she was given small doses of morphine. On Nov 20, 1935, she was given her fifth treatment in the hypertherm. Examination before treatment revealed nothing new. The pulse rate was 90, the blood pressure 130 systolic and 70 diastolic and the rectal temperature 98.6 F.

- 11 00 a m Patient placed in Kettering hypertherm
- 11 15 a m Temperature, 101 F, pulse rate, 110, patient noisy, restless and hyperactive, morphine, $\frac{1}{6}$ grain (0.01 Gm), subcutaneously

⁶ Histologic examination did not confirm the diagnosis of dementia paralytica. Neither perivascular infiltration nor neuronal atrophy was encountered.

- 12 00 m Temperature, 106 F , pulse rate, 142, current turned off , patient left in cabinet covered with terry cloth towels
- 12 15 p m Temperature, 106.6 F , pulse rate, 150, in view of the rising temperature, patient was uncovered, intake of fluid, 800 cc
- 12 25 p m Temperature, 107.4 F , pulse rate, 158, cyanosis of lips, ears and nail beds, fans directed on body, body sprayed with lukewarm water, fibrillation of heart
- 12 30 p m Temperature, 107.4 F , pulse rate, 153, fibrillation continued
- 12 36 p m Blood pressure, 60 systolic and 30 diastolic, pulse rate, 150
- 12 46 p m Temperature 107 F , Pulse rate, 150, intravenous infusion of 0.9 per cent saline and 9 per cent dextrose solution started, cardiac irregularity continued
- 12 49 p m Blood pressure, 60 systolic and 40 diastolic, pulse rate, 148, difficult to make out whether heart was fibrillating or whether there were extrasystoles, patient comatose, cyanosis of finger-tips
- 12 58 p m Temperature, 106.4 F , pulse rate, 156, blood pressure, 60 systolic and 40 diastolic, frequent extrasystoles at apex of heart
- 1 05 p m Temperature 106.4 F , pulse rate, 146, cyanosis of finger-tips persisted, inhalations of 5 per cent carbon dioxide and oxygen given by mask, with some relief of cyanosis, profuse discharge of yellowish white material from mouth
- 1 12 p m Temperature, 104.6 F , pulse rate, 140, blood pressure, 80 systolic and 60 diastolic, respiratory rate, 28, drooling of secretions from mouth continued
- 1 25 p m Temperature, 104 F , pulse rate, 126, blood pressure, 80 systolic and 40 diastolic
- 1 30 p m 1,000 cc of fluids already given intravenously, temperature, 104 F , pulse rate, 132, respiratory rate, 28, coarse bubbling rales at base of both lungs, more pronounced on left
- 1 38 p m Pulse rate, 128, blood pressure, 110 systolic and 30 diastolic, cyanosis of finger-tips persisted
- 1 47 p m Temperature, 102 F , pulse rate, 116, blood pressure, 130 systolic and 20 diastolic, respiratory rate, 28, patient still comatose
- 1 56 p m Pulse rate, 114, blood pressure, 135 systolic and 30 diastolic, skin, cool, cyanosis of nail beds
- 2 00 p m 1,500 cc of fluids already given intravenously, temperature, 103 F , pulse rate, 116, rigidity of lower extremities and left arm, flexion of fingers and toes on left, pupils, dilated, left greater than right, drooping of left lid and left side of mouth
- 2 14 p m Temperature, 103 F , repetition of seizure, with marked rigidity lasting eleven minutes, rigidity of left upper and lower extremities, weakness of right upper extremity and flexion of fingers and wrist
- 2 27 p m Temperature, 103.8 F , pulse rate, 120, blood pressure, 118 systolic and 60 diastolic, coma continued, skin, pale
- 2 45 p m Temperature, 104 F , pulse rate, 120, blood pressure, 86 systolic and 50 diastolic

- 3 00 p m Temperature, 104 F , pulse rate, 136, blood pressure, 85 systolic and 48 diastolic, inhalations of oxygen and 5 per cent carbon dioxide given for ten minutes, as breathing was labored, with occasional periods of apnea
- 3 02 p m Intravenous infusion of 0.9 per cent saline and 10 per cent dextrose solution started
- 3 12 p m Temperature, 104 F pulse rate, 136
- 3 15 p m Pulse rate, 120, blood pressure, 88 systolic and 42 diastolic, patient, comatose, skin warm, good color except for slight cyanosis of nail beds
- 3 30 p m Only 900 cc of solution given intravenously, as breathing became labored, temperature, 103.6 F , pulse rate, 134, inhalations of oxygen and 5 per cent carbon dioxide for ten minutes
- 3 40 p m Pulse rate, 120, blood pressure, 112 systolic and 60 diastolic
- 3 50 p m Pulse rate, 148, temperature, 103.6 F , blood pressure, 150 systolic and 74 diastolic, respiratory rate, 20, Babinski reflex on left
- 4 05 p m Temperature, 103.4 F , pulse rate, 126, blood pressure, 106 systolic and 60 diastolic, epinephrine, 12 minims (0.74 cc), subcutaneously
- 4 14 p m Catheterization of bladder, 155 cc of urine obtained, no sugar, diacetic acid or acetone
- 4 17 p m Patient vomited 1 pint (475 cc) of foul-smelling material
- 4 25 p m Temperature, 102.6 F , pulse rate, 112, blood pressure, 100 systolic and 60 diastolic, involuntary, foul dejecta
- 4 42 p m Temperature, 102.6 F , pulse rate, 111, blood pressure, 102 systolic and 58 diastolic
- 5 15 p m Temperature, 102.8 F , pulse rate, 108, blood pressure, 70 systolic and 50 diastolic
- 5 20 p m Epinephrine, 8 minims (0.5 cc), subcutaneously, pulse rate, 120, blood pressure, 70 systolic and 50 diastolic
- 5 26 p m 50 cc of 50 per cent solution of dextrose given intravenously, with 8 units of insulin subcutaneously, convulsive seizure occurred, turning of head to left and clonic and tonic movements of left upper extremity, Babinski sign on left
- 5 30 p m Blood pressure, 82 systolic and 60 diastolic, patient, comatose, involuntary dejecta
- 6 00 p m Recurrence of convulsive seizures, involuntary dejecta
- 6 17 p m Cessation of convulsions, pulse rate, 96, blood pressure, 112 systolic and 80 diastolic, labored breathing, coughing
- 6 22 p m Epinephrine, 8 minims (0.5 cc), caffeine with sodium benzoate, 5 grains (0.3 Gm), subcutaneously, repeated generalized convulsions, pulse rate, 120
- 6 30 p m Temperature, 103.8 F , pulse rate, 108, blood pressure, 110 systolic and 68 diastolic
- 6 45 p m Temperature, 103.8 F , pulse rate, 104, blood pressure, 80 systolic and 56 diastolic, respiratory rate, 24, patient, quiet, hands, cold and cyanotic

- 6 55 p m Temperature, 104 F , pulse rate, 108, blood pressure, 86 systolic and 60 diastolic, respiratory rate, 25, restlessness and groaning, mild generalized convulsion, head turned to the left, drooping of left side of mouth
- 7 05 p m Temperature, 104.2 F , pulse rate, 100, blood pressure, 82 systolic and 62 diastolic, hands, cold, nail beds, cyanosed, respirations, stertorous, with rate of 26
- 7 15 p m Blood pressure, 80 systolic and 62 diastolic, epinephrine and caffeine repeated
- 7 30 p m Blood pressure, 98 systolic and 60 diastolic, pulse rate, 104, temperature, 104.6 F , hands, cold and cyanotic
- 7 45 p m Pulse rate, 120, blood pressure, 96 systolic and 62 diastolic, respirations, deep, with rate of 20, atropine, $\frac{1}{150}$ grain (0.4 mg), for tracheal râles
- 7 50 p m Temperature, 104.8 F , pulse rate, 120, blood pressure, 78 systolic and 52 diastolic, respiratory rate, 40, sponging of body followed by convulsive seizures, groaning, resistance to handling, incontinence of urine and feces, vomiting of considerable amount of green watery material
- 7 57 p m Temperature, 103.8 F , pulse rate, 120 and irregular, tracheal râles, blood pressure, 84 systolic and 52 diastolic
- 8 10 p m Pulse rate, 120, blood pressure, 68 systolic and 44 diastolic, vomiting of green, foul-smelling material, temperature, 104.6 F , respiratory rate, 40 and labored, involuntary movements of bladder and bowel, twitchings of circumoral muscles, caffeine and epinephrine administered
- 8 20 p m Pulse rate, 112, blood pressure, 52 systolic and 40 diastolic, respiratory rate, 40, complete ptosis of left upper lid
- 8 30 p m Pulse rate, 130, blood pressure, 58 systolic and 40 diastolic
- 8 50 p m Pulse rate, 112, blood pressure, 58 systolic and 40 diastolic, restlessness and groaning, many coarse râles scattered over both lungs
- 9 15 p m Pulse rate, 120, blood pressure, 54 systolic and 40 diastolic, incontinence of urine and feces
- 9 20 p m Caffeine and epinephrine subcutaneously, inhalations of oxygen and 5 per cent carbon dioxide
- 9 30 p m Temperature, 105.4 F , pulse rate, 140, respiratory rate, 46, blood pressure, 52 systolic and 40 diastolic, great restlessness
- 9 50 p m Scopolamine hydrobromide, $\frac{1}{100}$ grain (0.6 mg), subcutaneously and paraldehyde, 2 cc, intramuscularly, inhalations of oxygen and 5 per cent carbon dioxide, mottled cyanosis of trunk
- 10 05 p m Pulse rate, 118, temperature, 104.8 F , blood pressure, 70 systolic and 50 diastolic, respiratory rate, 48, improved color of skin
- 10 25 p m Temperature, 104.4 F , pulse rate, 118, respiratory rate, 50, blood pressure, 72 systolic and 58 diastolic, mild convulsions
- 10 40 p m Temperature, 104.2 F , pulse rate, 110, blood pressure, 74 systolic and 52 diastolic, great restlessness, respiratory rate, 48, hands, cyanotic and cold, breathing, stertorous, with many tracheal râles

- 11 00 p m Catheterization, normal urine, blood pressure, 70 systolic and 50 diastolic, pulse rate, 110 and irregular
- 11 25 p m Temperature, 103.4 F, pulse rate, 110 and irregular, blood pressure, 76 systolic
- 11 45 p m Temperature, 103.8 F, pulse rate, 110, blood pressure, 74 systolic and 56 diastolic, labored respirations, with rate of 48, pupils, round and equal, no reaction to light, reflexes of biceps and radial muscles, active and equal, no triceps, patellar or ankle jerks, suggestive Babinski sign on right
- 12 00 m Temperature, 103 F, pulse rate, 108, respiratory rate, 46, blood pressure, 70 systolic, pulse irregular, marked cyanosis, atropine, $\frac{1}{100}$ grain (0.6 mg), subcutaneously for pulmonary edema
- 12 20 a m Temperature, 103 F, pulse rate, 110, blood pressure, 80 systolic and 50 diastolic, cyanosis
- 12 45 a m Temperature, 103 F, pulse rate, 104 and irregular, blood pressure, 75 systolic
- 1 10 a m Blood pressure, 70 systolic and 50 diastolic, cyanosis of nail beds marked, caffeine and epinephrine subcutaneously, inhalations of oxygen and 5 per cent carbon dioxide, poor condition
- 1 20 a m Temperature, 104 F, blood pressure, 70 systolic, caffeine, epinephrine and carbon dioxide and oxygen repeated
- 1 35 a m Pulse rate, 120, respiratory rate, 44, aspiration of trachea because of râles, blood-tinged fluid obtained
- 2 00 a m Pulse rate, 144, temperature, 104 F, increase of cyanosis, pulse of poor quality
- 2 10 a m Pulse rate, 132, blood pressure, 60 systolic, respiration, shallow, with rate of 40, caffeine, epinephrine and carbon dioxide and oxygen repeated, respirations ceased

The outstanding observations in this case were vascular collapse with cardiac arrhythmia, coma, convulsions with neurologic changes, loss of sphincteric control and pulmonary edema. The blood pressure rose after stimulation, the intravenous administration of fluids and inhalations of 5 per cent carbon dioxide and oxygen, only to fall again rapidly. Permission for postmortem examination was granted.

The autopsy was performed by Dr. Anna Allen, and the histologic examination was made by Dr. Myrtelle M. Canavan, who gave us permission to publish a summary of the data.

Gross Postmortem Examination—Both ankles were edematous. The fat over the thorax and abdomen was pale and edematous. There was continuous oozing of liquid blood from the cut surface of the abdomen and thorax. The muscles were somewhat pale. Many adhesions were noted between the omentum, the intestines and the anterior abdominal wall. The intestines were somewhat distended and deeply injected, and there was also a small amount of slightly blood-tinged fluid in the abdominal cavity. There were old adhesions at the apex of both lungs but no free fluid in the pleural cavities. The bronchial mucosa was somewhat injected, and the bronchi contained a small amount of frothy fluid.

Lungs The left lung weighed 400 Gm. On section slight edema and slight diffuse congestion were noted and were more marked in the dependent portion. The right lung weighed 490 Gm and showed more edema than did the left lung. In the lowest lobe there were scattered patchy hemorrhages.

Heart The heart weighed 330 Gm. The epicardial fat was fairly abundant, pale and somewhat edematous. There was slight diffuse thickening of the epicardium. The free edge of the mitral valve was rolled over, thickened and wrinkled. Slight thickening at the base of the aortic cusps was present. The other valves were normal. The endocardium lining the left ventricle was slightly thickened, and a few subendocardial hemorrhages were present. The myocardium was somewhat pale but firm. There was an occasional patch of thickening in the aorta above the valve. The right coronary artery showed a few atheromatous plaques. The left coronary artery also showed some atheromatous changes.

Gastro-Intestinal Tract The stomach mucosa was discolored and slightly swollen and that of the duodenum was injected. The mucosa of the jejunum was intensely swollen and hemorrhagic, it contained blood-stained liquid, as did the upper part of the ileum. At the ileocecal valve there were three hemorrhagic areas in the mucosa.

Liver The liver weighed 1,830 Gm and was soft and flabby. There were irregular patches of congestion and many light yellowish patches on the surface. The outlines of the lobules were blurred and swollen. Fatty changes were present throughout.

Kidneys The right kidney weighed 170 Gm, and the left kidney 160 Gm. Both were normal except for the suggestion of cloudy swelling.

Adrenals The right adrenal gland measured 4 by 4.5 by 1 cm. On section the center of the right adrenal gland was seen to be completely softened, with a large cavity. The cortex was thin and light yellow. The left adrenal gland measured 5.5 by 3 by 1 cm. The center of the medulla was firm and dark brown.

Brain There was a small subdural hemorrhage, about 1 cm in diameter, over the temporal region. The dura was adherent in the frontal region and thickened and tensely stretched over the brain. The dura over the right temporal region was more markedly thickened than elsewhere, and there was beginning membrane formation. Underneath the fairly recent hemorrhage the dura was stained yellow. The brain weighed 1,200 Gm. The pia mater over the vertex of the brain was moderately thickened, and there was intense injection of the pial blood vessels. Subdural blood, fairly recent (within twenty-four hours probably), was present in the middle fossa and over part of the tentorium cerebelli on the right side. There was a marked pressure cone, formed by the cerebellum around the medulla. The arteries at the base showed slight diffuse thickening, and in the basilar artery there was fusiform dilatation in the portion situated over the lower part of the pons. This aneurysmal dilatation extended for 1 cm. There was granular ependymitis in the floor of the fourth ventricle. The fourth ventricle was dilated.

The brain was fairly firm. On palpation, however, the pons appeared softer than the spinal cord. There was also a loss of consistency over the lateral ventricle, suggesting internal hydrocephalus.

Histologic Postmortem Examination—The histologic examination, as summarized by Dr. Canavan, revealed the following information:

The heart was edematous and slightly fibrotic. The lungs showed edema, hyperemia, hemorrhages and exudations of various ages. The spleen presented some hyperemia of the vessels and moderate collections of lymph around the vessels. The liver showed cloudy swelling, periductal infiltration and hyperemia. The kidneys were hyperemic, and there was slight tubular degeneration. The adrenal glands showed slight degeneration of the cells, especially in the zona fasciculata. The stomach and small intestines were hyperemic and edematous. The brain showed chronic meningitis, subarachnoid hemorrhages, some thickening of the vessels in the subarachnoid space and subependymal gliosis in the basal ganglia.

COMMENT

An examination of the observations made shows that in hyperpyrexia induced by hot moist air there are disturbances in four mechanisms of the Blalock classification ^{1a} by means of which shock, or acute failure of the circulation, may occur

- 1 Hematogenic—due to the reduction of the volume of blood
- 2 Vasogenic—due to the effect of heat per se on the capillaries
- 3 Neurogenic—due to stimuli acting through the nervous system
- 4 Cardiogenic—a probable but not an important factor

Hyperpyrexia induced by hot moist air causes (chart 1)

- I A diminished total blood volume which leads to
 - A A slowing of the blood flow and a diminished venous return, causing a lessened cardiac output and resulting in
 - a Relative anoxemia, which in turn leads to
 - 1 Increased capillary permeability with
 - 2 Further reduction in the blood volume
- II A probable direct effect on the capillary endothelium, resulting in increased capillary permeability
- III An increase in the metabolic rate requiring an increased supply of blood and oxygen, i e, a greater demand under adverse conditions, and tending to cause
 - A A further rise in the body temperature
- IV Interference with the absorption of fluids from the gastro-intestinal tract, making it difficult to offset the loss of fluids from sweating
- V A probable increase in the output of epinephrine, resulting in
 - A Constriction of the precapillary vessels already constricted and leading to
 - a Further reduction in blood flow
 - 1 Greater anoxemia
 - 2 Increased capillary permeability
- VI A possible effect on the nervous system
 - A Through changes in the brain cells as a result of hyperpyrexia per se, partial anoxemia and disturbance in the p_H of the blood
 - B A lessened and disturbed control by the central temperature mechanism
 - C Increased intracranial pressure as a result of cerebral edema
 - D Disturbances in respiration due to
 - a Alkalosis
 - b Increased intracranial pressure
 - c Anoxemia

Blood Volume—Investigations ⁷ of patients in this clinic during hyperpyrexia induced by hot moist air under conditions similar to those for the group of patients reported on here have revealed by the dye method of Gregersen and his co-workers ⁸ that there is invariably a

⁷ This work was completed in our clinic in conjunction with Drs J G Gibson 2d and W A Evans Jr and is now ready for publication

⁸ Gregersen, M I, Gibson, J J, and Stead, E A Plasma Volume Determination With Dyes, *Am J Physiol* **113** 54 (Sept) 1935

reduction in the volume of blood plasma, ranging from 10 to 32 per cent, accompanied with increases in the hematocrit values of from 3 to 9 per cent

In one patient (J P of the group under discussion) who was exposed to the hypertherm over a period of two and three quarter hours and in whom the temperature level fluctuated for an additional two and

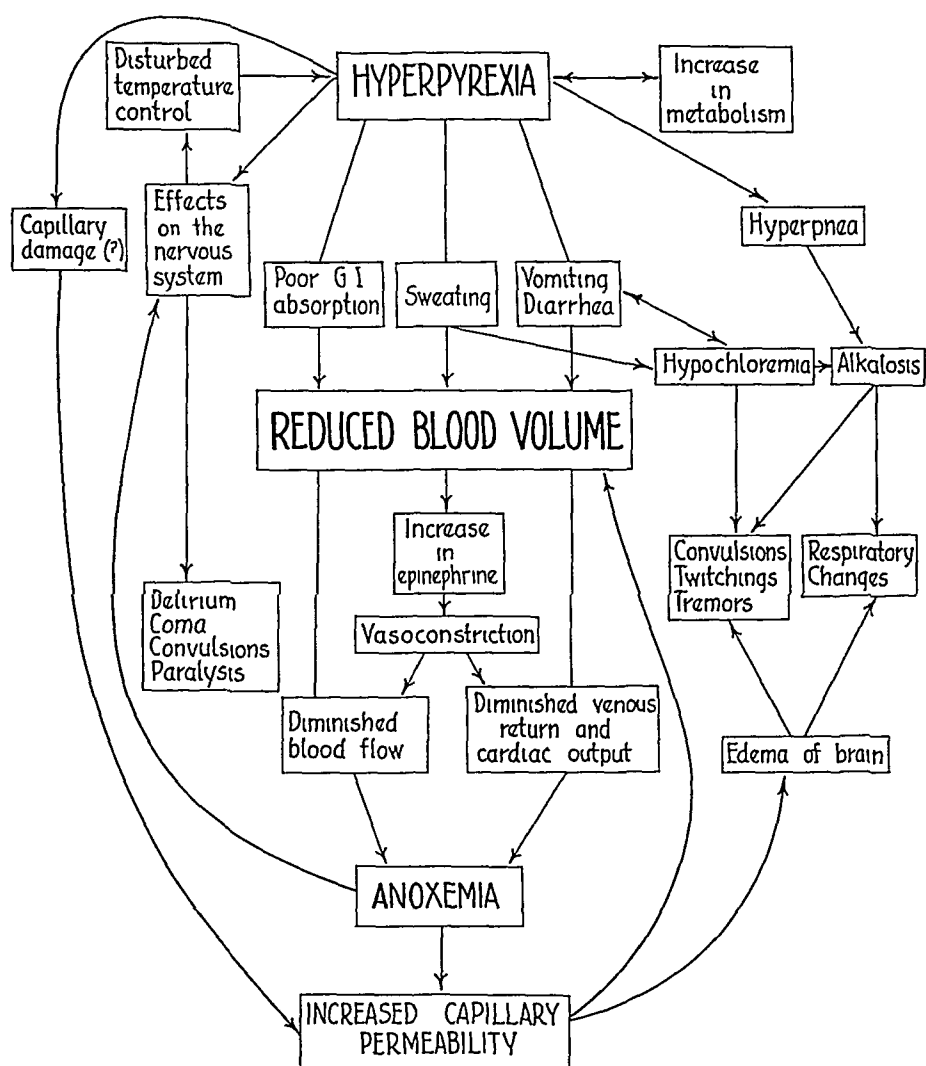


Chart 1—The mechanism of shock in therapeutic hyperpyrexia

one quarter hour between 105 and 106 F, the volume of blood plasma was reduced as much as 32 per cent, even though the intake of fluid during the entire period was 3,000 cc of 0.4 per cent saline solution. The loss in body weight, representing fluids lost as a result of treatment, was 1¼ pounds (0.6 Kg). This patient did not go into shock. In a second patient (H H) shock resulted on two occasions when the plasma volume was reduced 21 and 27 per cent at temperature levels of 106.4

and 105.6 F, respectively, after exposures of two and three hours. The intake of fluid was less than 500 cc of saline solution on each occasion, and the loss in body weight was 6½ and 7½ pounds (3 and 3.5 Kg), respectively. In a third patient (J. S.) the body temperature was raised to 105 F in one and five-sixth hours and was prolonged for nearly two hours at a level ranging from 105 to 106.1 F. An intake of 750 cc per hour of 0.6 per cent saline solution was recorded during the rise, prolongation and fall in the body temperature, making a total intake of 4,000 cc. Despite a gain of 4¼ pounds (2 Kg) in the body weight, the plasma volume showed a maximum concentration of 12.5 per cent.

Further confirmation of the finding of a reduced volume of blood by the method used is afforded by the following observations.

One of the patients (H. H.) in whom shock occurred at a temperature of 106.4 F, with a diminution in the plasma volume of 21 per cent, had an increase in the plasma volume to about the original level (6 per cent concentration) after an intravenous infusion of 1,350 cc of 0.9 per cent saline and 10 per cent dextrose solution (chart 2). The hematocrit value, which had increased from a basal level of 45 to 51.5 per cent at the height of blood concentration, fluctuated from 45.5 to 47 per cent during and after the intravenous infusion.

One deduces the importance of the blood volume from the observations of Hartman and Major⁹ in experiments on dogs. The animals were given morphine or sodium amytal, and the body temperature was raised and maintained at levels from 108 to 109 F for from seven to nine hours by means of the Kettering hypertherm. Two bouts of fever were given in thirty-six hours. Only the animals which received repeated intravenous infusions of dextrose or mixtures of dextrose and saline solution survived. On the other hand, despite the ingestion of an amount of saline solution by mouth equivalent to the amount of salt and water lost during the procedure, the animals not receiving intravenous infusions died as a result of vascular collapse.

Because of the concentration of blood there occurs slowing of circulation, an insufficient venous return and a diminished cardiac output. The blood supply of the capillaries is interfered with, and capillary dilatation becomes more marked, because of a lack of oxygen, a diminished supply of the "tonic hormone" secreted by the pituitary gland¹⁰ or an insufficient blood supply to the vasomotor center in the brain.¹¹

9 Hartman, F. W., and Major, R. C. Pathological Changes Resulting from Accurately Controlled Artificial Fever, *Abstr. of Papers, Ann. Fever Conf.*, 1935, p. 67, *Am. J. Clin. Path.* 5: 392 (Sept.) 1935.

10 Krogh, A. *The Anatomy and Physiology of Capillaries*, New Haven, Yale University Press, 1924, p. 258.

11 Harrison,^{1d} p. 19.

The reduction in the blood volume is evidently not the only important factor concerned in our series. Marked concentration of the blood plasma, which, at a temperature of 106 F or above was accompanied with shock, has been found in the same patient at lower body tempera-

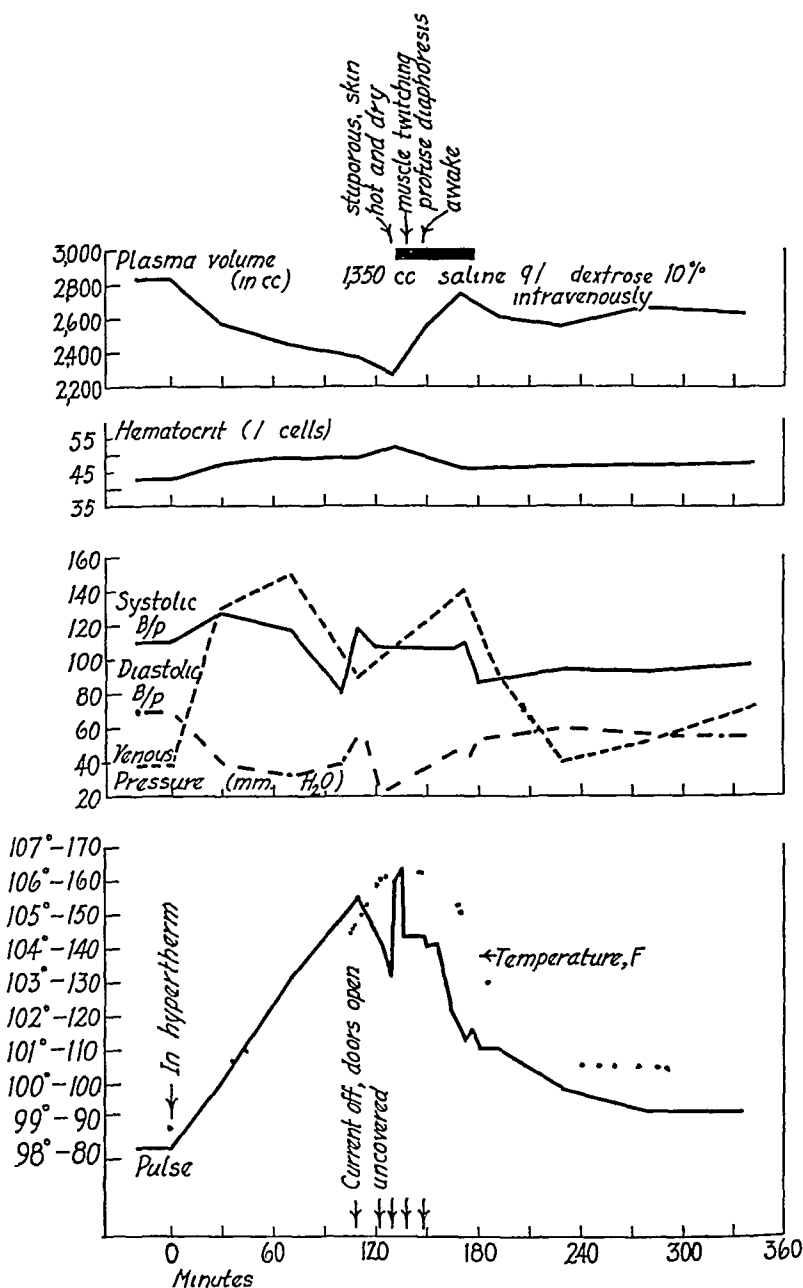


Chart 2—The concomitants of shock occurring in hypertherm hyperpyrexia plasma volume, hematocrit readings, arterial and venous blood pressures, pulse rate and body temperature, showing the changes induced by intravenous infusion and cooling the body

tures without shock ⁷ Talbott ⁴ has found marked concentration of the blood in patients exposed to high dry temperatures in whom heat cramps occurred, while few other constitutional symptoms were present. Only slight rises in the body temperature of these patients occurred.

The permeability of the lymphatic capillaries has been found to be increased when the temperature of the part is raised ¹². The edema of the hands seen occasionally after hyperthermia hyperpyrexia is indicative of altered capillary permeability. Krogh has stated that normally the permeability of the capillaries is increased by dilatation and, as a general rule, those physical and chemical agents which give rise to capillary dilation will also, when applied in sufficient strength, cause edema or stasis or both ¹³. Artificial fever, induced by high external temperatures with the prevention of loss of heat, is an ideal dilator of the capillaries and must be included in the group of physical agents specified by Krogh. The increase in capillary permeability due to the effect of heat per se and anoxemia causes a still further reduction in the blood volume, and a vicious circle is thus produced ¹⁴. The microscopic examination of the tissues in our fatal case revealed vasodilatation and increased capillary permeability, as shown by the edema of the heart, edema, hyperemia, hemorrhages and exudates of the lungs, hyperemia of the liver and kidneys, hyperemia and edema of the gastro-intestinal tract, and edema, hemorrhages and hyperemia of the brain and its membranes.

Metabolic Rate—An increase in the metabolic rate of from 5 to 14 per cent for each degree of rise in temperature has been found in therapeutic hyperpyrexia ¹⁸. It has also been observed that the increment of rise in the metabolic rate per degree of fever tends to increase

12 Hudack, S. S., and McMaster, P. D., cited by Bierman, W. Radiotherapy Fever Induced by Short Radio Waves, *Arch. Phys. Therapy* **13** 389 (July) 1932.

13 Krogh, ¹⁰ pp. 232 and 235.

14 The use of sedatives of the morphine and barbituric acid series during hyperthermia hyperpyrexia is dangerous. The combined capillary dilator effects of fever and of the anesthetic may result in marked loss of tone, with greater liability of shock ¹⁵. The rise in temperature is more rapid, ¹⁶ the control of the temperature is more difficult and the water shifting mechanism is disturbed ¹⁷. Sodium amytal may produce capillary damage ⁹.

15 Krogh, ¹⁰ p. 125.

16 Sheard, C. Thermal Changes Produced in Various Tissues of Animals by Systemic and Local Applications of Radiotherapy, *Abstr. of Papers, Ann. Fever Conf.*, 1935, p. 42.

17 Barbour, H. G. Heat Regulation and Water Exchange. The Effects of Hot and Cold Baths upon Blood Concentration and Brain Volume in Dogs, *Am. J. Physiol.* **67** 366, 1924.

18 Kopp, I. Metabolic Rates in Therapeutic Fever, *Am. J. M. Sc.* **190** 491 (Oct.) 1935.

sharply at levels of 106 F and above¹⁹ It is obvious therefore that the demands on the organism are greater at these levels of temperature at a time when the volume of blood is considerably reduced, the circulatory rate diminished and oxygenation interfered with The increased metabolism creates more heat in the body, while the dissipation of heat by evaporation of sweat from the surface of the skin is greatly impeded by dehydration and by the high dry and wet bulb temperatures surrounding the body

Impaired Absorption of Fluids—Absorption of fluid from the gastro-intestinal tract during hypertherm hyperpyrexia is either delayed or impaired, as revealed by our own experiments and by the work of Hartman and Major⁹ It is further confirmed by the following observations

1 The blood volume remains below normal, despite the taking of large quantities of fluid by mouth, even though there is an increase in body weight during treatment

2 The blood volume can be maintained at a normal level only by continuous intravenous infusion of large amounts of fluid⁷

3 The amount of fluid vomited during therapy in many instances is as great as the total intake of fluid over a period of one or two hours

Increased Output of Epinephrine—An increase in the output of epinephrine is suggested by marked rises in systolic blood pressure and pulse rate both during the ordinary course of fever and just prior to shock For example, in the patient (H H) in whom shock occurred at a temperature of 106.4 F, with a plasma concentration of 21 per cent, a rapid increase in the pulse rate from 132 to 164 and a rise in systolic blood pressure from 80 to 118 mm were noted before the reaction occurred (chart 2) Marked rises in the systolic blood pressure as high as 300 mm and in the pulse rate to 180 per minute have been noted in other patients at temperature levels of 106 F or higher during the ordinary course of fever treatment Experimental evidence has been offered by Freeman and his co-workers²⁰ that dehydration increases the output of epinephrine He reasoned that partial asphyxia results from the diminution in blood volume, increase in blood viscosity and diminution in blood flow due to dehydration and that these factors are responsible for an increase in the output of epinephrine Microscopic examination of the adrenal glands of our patient and of others reported on in the literature as having died as a result of hypertherm hyperpyrexia

¹⁹ Kopp, I Unpublished data

²⁰ Freeman, N E, Morison, R S, and Sawyer, M E M Effect of Dehydration on Adrenal Secretion and Its Relation to Shock, *Am J Physiol* **104** 628 (June) 1933

revealed degeneration of cells, especially in the zona fasciculata Cramer²¹ has pointed out that the postmortem pictures of heat stroke were typical of hyperaction followed by exhaustion of the thyroid and the adrenal glands

The increased output of epinephrine during shock due to hyperpyrexia exaggerates the state of shock by reducing still further a diminished blood volume²² Vasoconstriction results—a condition which is already present during these reactions and which, if beyond an optimal degree, aggravates the circulatory failure by interfering with the venous return to the heart, which is already inadequate, and thus the cardiac output is still further reduced²³ The anoxemia thereupon is more marked, and the capillary permeability is increased

The Presence of a Neurogenic Factor—It seems almost obvious that the nervous mechanism plays a distinct rôle in shock due to hypertherm fever, but in the present state of knowledge it is not possible to evaluate its rôle correctly It is probable that both the autonomic and the cerebral nervous system are implicated

It is generally recognized that stimulation of the sympathetic system is capable of producing shock For example, shock occasionally occurs after a bullet wound, a blow in the solar plexus or coronary thrombosis, which lead to extreme vasodilatation²⁴ It has already been stated that hypertherm hyperpyrexia, by causing dehydration, stimulates the sympathico-adrenal system²⁰ It is also recognized that changes in environmental temperature and humidity cause activity of the sympathetic system in an attempt to meet the exigencies of the situation²⁵ When the demand on this system is too great or too sudden, a breakdown occurs In our experience there is a distinct relationship between the wet bulb temperature and bad reactions Certainly, the patient's discomfort is definitely related to this factor Vomiting occurs much more frequently when the wet bulb level is high than when it is low Shock phenomenon in our patients occurred only when they were in the hypertherm, where the wet bulb temperature approximates 135 F, and never in the diathermy-carbon lamp machine, where it is about 105 F This is in consonance with the well known fact that a high external temperature with a low humidity is well tolerated²⁶ Haldane has clearly demonstrated that severe reactions depend on the height of

21 Cramer, W, cited by Hill⁵

22 Gibson, J G Personal communication to the authors Erlanger, J, and Gasser, H S, cited by Moon^{1b}

23 Eggleston, C The Pharmacopeia and the Physician Drugs Used in the Treatment of Circulatory Failure in Acute Infectious Diseases, J A M A **107** 1213 (Oct 10) 1936

24 Blalock^{1a} Harrison^{1d} Atchley^{2a}

25 McConnell, W J Correlation of Skin Temperatures and Physiological Reactions, Am J Soc Heat & Vent Engin **30** 457, 1924

26 Haldane, J S Influence of High Air Temperatures, J Hyg **5** 494, 1905

the absolute wet bulb level²⁶ Likewise Hall and Wakefield²⁷ showed that the time necessary to produce heat stroke in dogs subjected to high humid temperatures was generally proportional to the height of wet bulb temperatures

The cerebral nerve cells are rather more readily damaged by high temperature than are less specialized cells of the body The cerebral ganglion cells of experimental animals which died as a result of hypertherm hyperpyrexia at temperatures ranging from 108 to 109 F showed shrinkage and pyknosis⁹ The temperature levels reached in some patients are not far below these levels and are near enough to suggest an interference in function if not in structure In addition to the temperature itself, the cerebral cells are exposed to relative anoxemia due to a diminution in blood volume Alkalosis is still another noxious state Evidence of disturbed function of the cerebral mechanism is frequently encountered in the treatments in the form of projectile vomiting and delirium In the shock reactions there are, in addition, coma, muscle tremors, muscle twitchings and convulsions

The symptoms of tetany that are occasionally seen are characterized by muscle rigidity, tonic and clonic convulsive seizures of the extremities and abdomen and fibrillary twitchings Alkalosis occurs in hypertherm hyperpyrexia²⁸ and is dependent on (a) a loss of carbon dioxide by hyperventilation and (b) a loss of chloride, due to excessive sweating Although sodium also is lost, this is not so important as the loss of carbon dioxide and chloride There is also some loss of chloride as a result of vomiting and diarrhea Some of the loss of sodium chloride is made up by the ingestion of saline solution by mouth, provided absorption takes place

Pathologic Observations—The pathologic observations made in our fatal case agreed essentially with those reported for two patients by Hartman and Major,⁹ with the exception that in their patients hemorrhagic encephalitis was present The other essential features are

- 1 Edema of the lungs, intestines and liver
- 2 Hyperemia of the intestines, liver, kidneys and spleen, congestion of the lungs and intense injection of the pial vessels
- 3 Subdural and subendocardial hemorrhages and hemorrhages of the lungs and intestines
- 4 Degeneration of the liver, tubular degeneration of the kidneys and vacuolar degeneration of the adrenal glands
- 5 A pressure cone around the medulla

²⁷ Hall, W W, and Wakefield, E G Study of Experimental Heat-Stroke, J A M A 89 177 (July 16) 1927

²⁸ Work completed in this clinic in conjunction with Drs M Pijoan and J G Gibson 2d and now ready for publication

These observations are similar to those for dogs in which fever was induced by means of the Kettering hypertherm,⁹ to those reported as typical of heat stroke,²⁹ and to those of the shock syndrome occurring under other conditions.^{1b} The edema, congestion and hemorrhages are due to the physiologic disturbances already described as occurring in hypertherm hyperpyrexia. The degeneration of tissue is probably due in great part to the height of fever and in a lesser degree to relative anoxemia and a change in the p_H of the blood.

Treatment—On the basis of the foregoing discussion, the treatment of shock due to hyperpyrexia must attempt to (1) reduce the body temperature, (2) overcome the dehydration and (3) remedy the alkalosis and hypochloremia. The following procedure is therefore carried out:

1 The patient is immediately removed from the fever cabinet and uncovered. The body surface is sprayed with lukewarm water, and evaporation is hastened by electric fans to reduce the body temperature rapidly. (The application of ice or cold water causes constriction of the surface capillaries and interferes with the loss of heat. Hill⁵ has stated that the evaporation of water at body temperature carries away 0.59 calories of heat per gram, while the melting of ice removes only 0.08 calories of heat per gram.)

2 Intravenous infusions of isotonic saline and 5 per cent dextrose solution in amounts ranging from 850 to 1,500 cc are given. Large amounts of fluid are necessary to raise the plasma volume to normal levels, but the dangers of overburdening the circulation with the production of pulmonary edema should be kept in mind, since this has been an important feature in fatal cases. Repeated determinations of the venous pressure should prevent this danger, but if pulmonary edema is present, small amounts of hypertonic solution are indicated.

The use of small amounts of hypertonic saline or dextrose solution to increase the blood volume to normal is of little value, since the body tissues are dehydrated and little fluid reserve is present that can be safely drawn on. It is true, however, that when hyperpyrexia is present, the patient is in collapse and the skin is hot and dry, the intravenous infusion of 100 cc of 50 per cent solution of dextrose is followed by some rise in the plasma volume, profuse diaphoresis and a fall in the body temperature.⁷ The patient, however, remains in a critical condition, the blood pressure is low, the pulse is rapid and the plasma volume falls again. Hypertonic solutions may have some value through their ability to reduce cerebral edema. The protracted use of hypertonic dextrose solution intravenously, however, is inadequate, since it tends to increase the intensity of shock by dehydration.^{2a}

29 Gauss, H, and Meyer, K. A. Heat Stroke. Report of One Hundred and Fifty-Eight Cases from Cook County Hospital, Chicago, *Am J M Sc* **154** 554 (Oct) 1917. Hill⁵

3 Inhalations of oxygen and 5 per cent carbon dioxide are given. This is an ideal respiratory stimulant, it supplies the body with carbon dioxide to compensate for the alkalosis, it reduces the cyanosis when present and it lessens the capillary permeability by relieving the anoxemia.

4 Paraldehyde by rectum and soluble phenobarbital U S P (sodium phenobarbital) intramuscularly are administered if the patient is extremely restless or if repeated convulsions occur.

5 When circulatory stimulants are indicated and when the aforementioned measures have not been successful, caffeine with sodium benzoate, $7\frac{1}{2}$ grains (0.5 Gm), is given subcutaneously every two hours. The use of epinephrine is now avoided for the reasons previously mentioned. Strychnine in large doses, $\frac{1}{20}$ to $\frac{1}{15}$ grain (3 to 4 mg), every two or three hours subcutaneously is advised by some,³⁰ since it tends to increase the blood volume, stimulate the oxidative processes and decrease the capillary permeability. Pitressin, 0.5 to 1 cc subcutaneously every three hours, is also commended, because of its ability to reduce capillary permeability.³⁰

SUMMARY

Evidence is presented that severe reactions and death as a result of hyperpyrexia induced by exposure to hot moist air with the prevention of loss of heat are due to the shock syndrome.

The mechanism of shock under these conditions consists of a diminution in the blood volume, an increase in the vascular bed and an increase in the vascular permeability.

A disturbed neurogenic mechanism, in addition to a disturbed hematogenic mechanism (dehydration), is also present.

The presence of alkalosis and hypochloremia during artificial hyperpyrexia modify the clinical picture of the shock syndrome.

The pathologic picture is similar to that observed in shock in other conditions and in heat stroke. Of especial importance is the presence of degenerative changes in the adrenal cortex.

A plan of treatment is offered in an attempt to reduce the body temperature, to increase the volume of blood, to diminish the capillary permeability and to compensate for the alkalosis and the loss of chlorides by (1) the evaporation of lukewarm water from the body surface, (2) intravenous infusions and (3) inhalations of carbon dioxide and oxygen.

IMMUNOLOGIC STUDIES OF SICKLE CELL ANEMIA

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With the exception of the work reported by Diggs¹ and that of Beck and Hertz,² practically none of the articles on sickle cell anemia published in the past five years includes investigative work on the subject. It seems that knowledge of the disease has reached an impasse at present and that all writing henceforth must consist of case reports and summarizations of the literature until a new stimulus arises to give further impetus to the study of the condition and an understanding of the facts at hand. The present information on this disease has done no more than give possible leads to the cause of the sickling phenomena. No one has yet found the cause, and, most important from the standpoint of the patient, no one has found an effective therapeutic regimen or agent that will materially help the patient in the active anemic stage of the disease. The challenge to medicine, therefore, still exists, and, as will be shown, the prevalence of cases of potential anemia is somewhat startling.

No attempt is made to summarize completely all the literature on sickle cell anemia since its description by Herrick³ twenty-six years ago. Articles with excellent summaries have been written by Steinberg⁴ and by Anderson and Ware⁵. For purposes of brevity here the pertinent facts that have been established appear to be adequate. Hahn and Gillespie⁶ have briefly listed the data from previous experimentations

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1 Diggs, L. W. Negative Results in the Treatment of Sickle Cell Anemia, *Am J M Sc* **187** 521 (April) 1934

2 Beck, J. P., and Hertz, C. S. Standardizing Sickle Cell Method and Evidence of Sickle Cell Trait, *Am J Clin Path* **5** 325 (July) 1935

3 Herrick, J. B. Peculiar Elongated and Sickle-Shaped Red Blood Corpuscles in a Case of Severe Anemia, *Arch Int Med* **6** 517 (Nov.) 1910

4 Steinberg, B. Sickle Cell Anemia, *Arch Path* **9** 876 (April) 1930

5 Anderson, W. W., and Ware, R. L. Sickle Cell Anemia, *Am J Dis Child* **44** 1055 (Nov) 1932, *J A M A* **99** 902 (Sept 10) 1932

6 Hahn, E. V., and Gillespie, E. B. Sickle Cell Anemia, *Arch Int Med* **39** 233 (Feb) 1927

on the condition up to 1927 Their summary is reproduced here together with the results of their own experiments and those of subsequent investigators

- 1 Sickle cell formation is retarded by cold and accelerated by heat (Sydenstricker ⁷)
- 2 Sickle cell formation is independent of exposure to light, although return to spherical shape is more rapid in the dark (Huck ⁸)
- 3 Serum is not essential to sickle cell formation, as the susceptible cells undergo the distortion when suspended in saline solution or citrated saline solution (Huck ⁸ and Hahn and Gillespie, ⁶ refuted by Sydenstricker ⁷)
- 4 Susceptible cells, washed, become sickle cells in normal serum of persons of the same blood type (Sydenstricker ⁷ and Huck ⁸)
- 5 Normal cells do not become sickle cells by the action of serum of a person whose blood contains sickle cells (Sydenstricker ⁷ and Huck ⁸)
- 6 Bile pigment and bile salts accelerate sickle cell formation (Sydenstricker ⁷)
- 7 Phagocytosis of sickle cells by large mononuclear cells occurs in vitro (Sydenstricker ⁷ and Emmel ⁹)
- 8 Large mononuclear cells of a person whose blood contains sickle cells do not phagocytose normal blood cells (Sydenstricker ⁷ and Emmel ⁹)
- 9 The production of sickle cells is inconstant in preparations made under identical conditions (Graham ¹⁰)
- 10 Sickle cells are observed in tissues of affected subjects taken post mortem when the tissues are fixed in solution of formaldehyde When Zenker's solution is used, sickle cells are not present (Graham and McCarty ¹¹)

After listing the foregoing data from previous investigations, Hahn and Gillespie reported their own investigations, which are now listed to continue the sequence of major facts available on sickle cell anemia

- 11 Sickle cell formation is induced when a suspension of susceptible cells in saline or citrated saline solution is placed in an atmosphere of carbon dioxide, nitrous oxide or hydrogen They will revert to the discoid form when the atmosphere is changed to diatomic oxygen or carbon monoxide
- 12 Acidification of a suspension of susceptible cells up to the point of beginning hemolysis favors the sickle cell reaction
- 13 A suspension of sickle cells buffered to a p_H of 6.8 in an atmosphere of ethylene will cause immediate sickling in five minutes, whereas in neutral solution this gas did not produce sickling

7 Sydenstricker, V P , Mulherin, W A , and Houseal, R W Sickle Cell Anemia, *Am J Dis Child* **26** 132 (Aug) 1923

8 Huck, J G Sickle Cell Anemia, *Bull Johns Hopkins Hosp* **34** 335 (Oct) 1923

9 Emmel, V E A Study of Erythrocytes in a Case of Severe Anemia with Elongated and Sickie-Shaped Red Blood Corpuscles, *Arch Int Med* **20** 586, (Oct) 1917

10 Graham, G S A Case of Sickie Cell Anemia with Necropsy, *Arch Int Med* **34** 778 (Dec) 1924

11 Graham, G S , and McCarty, S H Notes on Sickie Cell Anemia, *J Lab & Clin Med* **12** 536 (March) 1927

During the same year that this work was done Josephs¹² reported his experiments on sickle cell anemia. The sequence is continued with his statement

- 14 Some plasma component exists in all specimens of blood which cause sickling, but only the cells of patients who show the sickling phenomena are susceptible to it

Josephs is credited by some authors with having made a discovery which Huck overlooked. His work, in any case, refuted that of Huck and of Hahn and Gillespie and supported that of Sydenstricker (see number 3 of the foregoing listed data). Hahn,¹³ however, later reported work which he claimed in turn refuted that of Josephs.

Little experimental investigation was reported on this disease between 1927 and 1932. Miyamoto and Korb¹⁴ reported the incidence of the sickling phenomena in 400 persons in St. Louis. To this may be added the series of patients tested by Cooley and Lee, Graham and McCarty and others, as will be subsequently shown. Complete reports of pathologic observations were made by Jaffé,¹⁵ Sydenstricker,¹⁶ Yater and Mollari¹⁷ and others. Most interesting was the report of a case by Cooley and Lee,¹⁸ which definitely refuted the statements of previous authors that sickle cells occur only in Negroes. They described an authentic case in a Greek child. Previous similar reports had been made (Castana,¹⁹ Archibald²⁰ and Stewart²¹), but each case was questioned as to its authenticity because of the possibility (which the authors did not rule out) of admixture of Negro blood. Subsequent to Cooley's article, many reports had been made of proved cases among non-Negroes,

12 Josephs, H. W. Sickle Cell Anemia, *Bull. Johns Hopkins Hosp.* **40** 77 (Feb.) 1927.

13 Hahn, E. V. Sickle-Cell (Drepanocytic) Anemia, *Am. J. M. Sc.* **175** 206 (Feb.) 1928.

14 Miyamoto, K., and Korb, J. H. Meniscocytes (Latent Sickle Cell Anemia). Its Incidence in St. Louis, South M. J. **20** 912 (Dec.) 1927.

15 Jaffé, R. Die Sichelzellenanämie, *Virchows Arch. f. path. Anat.* **265** 452, 1927.

16 Sydenstricker, V. P. Sickle Cell Anemia, *M. Clin. North America* **12** 1451 (March) 1929.

17 Yater, W. M., and Mollari, M. The Pathology of Sickle-Cell Anemia. Report of a Case with Death During an "Abdominal Crisis," *J. A. M. A.* **96** 1671 (May 16) 1931.

18 Cooley, T. B., and Lee, P. Sickle Cell Anemia in a Greek Family, *Am. J. Dis. Child.* **38** 103 (July) 1929.

19 Castana, V. Gigantocytes and Sickle Cells, *Pediatrics* **33** 431 (April 15) 1925.

20 Archibald, R. G. Sickle Cell Anemia in the Sudan, *Tr. Roy. Soc. Trop. Med. & Hyg.* **19** 389 (Jan.) 1926.

21 Stewart, W. B. Sickle Cell Anemia. Report of Case with Splenectomy, *Am. J. Dis. Child.* **34** 72 (July) 1927.

for instance those by Sights and Simon,²² Rosenfeld and Pincus,²³ Cooke and Mack,²⁴ Pollock and Dameshek²⁵ and Wallace and Killingsworth²⁶ Several cases in which splenectomy was used in treatment of the disease were reported by Bell²⁷ (including that of a patient operated on by Cooley and Lee), Hahn¹³ and Ching and Diggs.²⁸ Penberthy and Cooley²⁹ reported in 1935 the results in 4 cases in which splenectomy was performed. One patient had been observed by them for six years. An interesting occasional finding of clinical interest is given in the reports submitted of osseous changes in the disease by Moore,³⁰ Vogt and Diamond,³¹ Brandau,³² de Castro³³ and Ginnan.³⁴ Recently Campbell³⁵ reported 6 cases in each of which there were acute abdominal manifestations, a symptom of which previous authors had made mention. Four of these patients were operated on, the findings were normal in 3 cases, and the fourth patient had cholecystitis and cholelithiasis. This fourth patient had a normal postoperative convalescence. The 2 patients who were not operated on had no symptoms a few days after admission to the hospital.

22 Sights, W. P., and Simon, S. D. Marked Erythrocytic Sickling in White Adults, Associated with Anemia, Syphilis and Malaria, *J. Med.* **12** 177 (June) 1931.

23 Rosenfeld, S., and Pincus, J. B. The Occurrence of Sicklemia in the White Race, *Am. J. M. Sc.* **184** 674 (Nov.) 1932.

24 Cooke, J. V., and Mack, J. K. Sickie-Cell Anemia in a White American Family, *J. Pediat.* **5** 601 (Nov.) 1934.

25 Pollock, L. H., and Dameshek, W. Elongation of Red Blood Cell in a Jewish Family, *Am. J. M. Sc.* **188** 822 (Dec.) 1934.

26 Wallace, S. A., and Killingsworth, W. P. Sicklemia in the Mexican Race, *Am. J. Dis. Child.* **50** 1208 (Nov.) 1935.

27 Bell, A. J., Mitchell, A. J., Cooley, T. B., and Lee, P. Sickie Cell Anemia. Report of Two Cases in Young Children in Which Splenectomy Was Performed, *Am. J. Dis. Child.* **34** 923 (Dec.) 1927.

28 Ching, R. E., and Diggs, L. W. Splenectomy in Sickie Cell Anemia, *Arch. Int. Med.* **51** 100 (Jan.) 1933.

29 Penberthy, G. C., and Cooley, T. B. Results of Splenectomy in Childhood, *Ann. Surg.* **102** 645 (Oct.) 1935.

30 Moore, S. Bone Changes in Sickie Cell Anemia with Note on Similar Changes Observed in Skulls of Ancient Mayan Indians, *J. Missouri M. A.* **26** 561 (Nov.) 1929.

31 Vogt, E. C., and Diamond, L. K. Congenital Anemias Roentgenologically Considered, *Am. J. Roentgenol.* **23** 625 (June) 1930.

32 Brandau, G. M. Sickie Cell Anemia. Report of a Case, *Arch. Int. Med.* **50** 635 (Oct.) 1932.

33 de Castro, A. S. Sickie Cell Anemia, *J. de pediat., Rio de Janeiro* **1** 427 (Nov.) 1934.

34 Ginnan, A. G. Roentgenologic Bone Changes in Sickie Cell and Erythroblastic Anemia, *Am. J. Roentgenol.* **34** 297 (Sept.) 1935.

35 Campbell, E. H., Jr. Acute Abdominal Pain in Sickie Cell Anemia, *Arch. Surg.* **31** 607 (Oct.) 1935.

Diggs³⁶ presented the first investigative report published since 1927, in which he attempted to show that the "rate of sickling is not related necessarily to the immediate severity of the anemia but to the chronicity of the anemia" He¹ was the first author to report an attempt at a therapeutic regimen with anywhere near an adequate number of patients, in that he described unsuccessful results of the treatment of 7 actively anemic patients using various antianemic agents In one other instance³⁷ the successful treatment of a patient with an acute abdominal crisis was reported, and other authors had previously reported the treatment of single patients with results contrary to those of Diggs

Perhaps the best contribution to the future investigative study of sickle cell anemia is the "standardizing sickle cell method" recently reported by Beck and Heitz² The method consists of fixing the red blood cells with solution of formaldehyde after they have been allowed to assume their characteristic sickle form in a test tube containing equal parts of physiologic solution of sodium chloride and 3 per cent solution of sodium citrate overlaid with liquid petrolatum The test is based on the observations previously reported by Hahn¹³ that solution of formaldehyde will fix the cells in the sickling deformity By this method, for a small series of patients these workers obtained a higher percentage of positive results (13 per cent) than has ever been reported They admitted, however, that this result must be verified by a larger series of tests

STATEMENT OF PROBLEM

After a survey of the literature it was found that with the exception of the few studies of blood grouping made on a small number of patients by Huck⁸ and later by Huck and Guthrie,³⁸ no one had made a study of the immunologic aspects of sickle cell anemia There are a number of facts that have led to the suggestion that an investigation of the immunologic properties of red blood cells having the sickling trait might be profitable The sickle cell phenomenon and the isohemo-agglutinating characteristics are each peculiar to red blood cells It has been definitely shown that each characteristic is inheritable That the inheritance of isohemo-agglutination has a definite racial distribution has been shown by Snyder,³⁹ who quoted the discovery by L Hirszfeld

36 Diggs, L W The Sickle Cell Phenomenon Rate of Sickling in Moist Preparations, *J Lab & Clin Med* **17** 913 (June) 1932

37 Torrance, E G, and Schnabel, T G Potassium Sulphocyanate A Note on Its Use for the Painful Crisis in Sickle Cell Anemia, *Ann Int Med* **6** 782 (Dec) 1932

38 Huck, J G, and Guthrie, C G On the Existence of More Than Four Iso-Agglutinin Groups in Human Blood, *Bull Johns Hopkins Hosp* **34** 37 (Feb) 1923

39 Snyder, L H Blood Grouping in Relation to Clinical and Legal Medicine, Baltimore, Williams & Wilkins Company, 1929

and H Hüsfield. He demonstrated that the blood type follows a definite racial index or frequency. It is not unreasonable, therefore, to imagine that constitutional factors might concomitantly affect both properties, since sickling of erythrocytes occurs for the most part among Negroes. In support of this idea was the suggestion made by Josephs¹² that further study of the disease from the standpoint of agglutination should be made, as well as the report by Huck and Guthrie,³⁸ who found anomalous iso-agglutinins in a patient with sickle cell anemia. An added stimulus to this method of study was the suggestion made by Landsteiner⁴⁰ of the possibility of an immune agglutinin in sickle cell anemia as a result of the work of Guthrie. Since Landsteiner⁴¹ and Wiener⁴² have already shown that the immune agglutinogens M and N are inheritable properties of red blood cells, the inclusion in this work of their method of study of these immune properties and of applying them to sickle cells is feasible. Another reason why this phase of study particularly applies here was given in the report by Landsteiner⁴³ that he had found a specific racial agglutinin in specimens of Negro blood. Investigation of this agglutinin was intended at first, but because of technical difficulties the idea had to be abandoned, and the study was confined to iso-agglutinogens and the immune factors M and N.

PROCEDURE

Patients whose red blood cells showed the sickling trait were located among those in the wards and in the clinic of the Provident and the Cook County Hospital by testing them as a routine when blood was being drawn for Wassermann tests. One drop of the blood collected in the syringe was placed in 2 cc of physiologic solution of sodium chloride. This suspension was used for typing the cells. Next the third finger of the left hand was cleansed with alcohol and pricked. A drop of this blood was used to make the test for sickling. The first 800 patients were tested by the well known cover glass and slide method. For the remaining tests in the total series the "standardizing sickle cell method" of Beck and Hertz² was used in addition to the other method. The cover glass was "ringed" with melted petrolatum which had first been drawn into a large medicine dropper. The dropper was passed through a flame as needed when the petrolatum did not flow easily. The slides were placed horizontally in a closed cabinet at room temperature and examined under the microscope the next morning.

40 Landsteiner, K. Personal communication to Dr. Julian H. Lewis, of the University of Chicago.

41 Landsteiner, K., and Levine, P. Individual Differences in Human Blood, *J. Exper. Med.* **47** 757 (May) 1928.

42 Wiener, A. S. Determination of Non-Paternity by Means of Blood Groups, *Am. J. M. Sc.* **186** 257 (Aug.) 1933.

43 Landsteiner, K., Strutton, W. R., and Chase, M. W. An Agglutination Reaction Observed with Some Human Bloods, Chiefly Among Negroes, *J. Immunol.* **27** 469 (Nov.) 1934.

The suspension of cells collected in physiologic solution of sodium chloride from each patient was typed, anti-A and anti-B serums prepared and standardized⁴⁴ in the laboratory being used. The standard laboratory technic for determining blood types was used. Examination of the mixture of cell suspension and serum was made both microscopically and macroscopically.

Every case of sickling encountered was rechecked at least once with a newly drawn specimen of blood. A double check on all the tests was possible when the Beck and Hertz method was included in the testing along with the cover slip method. In performing the Beck and Hertz test, 1 drop of the blood to be tested was added to a small test tube containing 1 cc of equal parts of physiologic solution of sodium chloride and 3 per cent solution of sodium citrate. After the blood was added the suspension was overlayed with liquid petrolatum, and the tube was allowed to stand overnight at room temperature. It was found, after a series of trials in known cases in which the results were occasionally inconsistent, that the saline-citrate solution must be acidified to a p_H of 6.9 (colorimetric method) to obtain consistently satisfactory results⁴⁵. Before the slide preparations were examined microscopically each morning, 0.5 cc of neutralized solution of formaldehyde was added beneath the layer of liquid petrolatum in each tube containing the saline-citrate suspension. The formaldehyde fixed the cells in whatever shape they had assumed, and after the slide preparation had been examined a drop of the cell suspension was withdrawn from beneath the layer of liquid petrolatum, placed under the microscope and examined for sickle cells.

For the preparation of the anti-M and the anti-N serums the Landsteiner technic⁴¹ was followed completely, with the exception of the method for testing the unknown specimens of blood. To avoid possible conflicting results because of the agglutininogen P in Negroes, only the immune serums produced by the injection of type O cells from white patients were used for routine testing. The immune serums obtained by the injection of blood from normal Negroes and from patients who showed sickling were used in special tests.

Since 20 or 30 specimens of blood were examined at one time, it was found more practical to substitute the Wiener⁴⁶ centrifugation method for the slide method of Landsteiner when testing for M and N agglutinogens. For each batch of blood studied, known specimens of M and N blood were used as controls. All the recordings of the results were made only as plus or minus.

The specimens of blood injected into rabbits were specimens for which the type either had been previously determined through the courtesy of Dr. Wiener or had been determined with absorbed serums furnished by him.

INCIDENCE OF SICKLING

Present Findings—The patients on whom these studies were made were found in the clinic and the wards of the Provident Hospital and the wards of the Children's Hospital and the men's medical wards of the Cook County Hospital. A total of 1,263 Negroes were tested. This

44 Coca, A. F. Slide Method of Titrating Blood-Grouping Sera, *J. Lab. & Clin. Med.* **16** 405 (Jan.) 1931.

45 Suggestions received from Dr. Beck, through personal correspondence, were of assistance on this particular point.

46 Wiener, A. S., Zinsher, R., and Selkowitz, J. The Agglutinogens M and N of Landsteiner and Levine, *J. Immunol.* **27** 431 (Nov.) 1934.

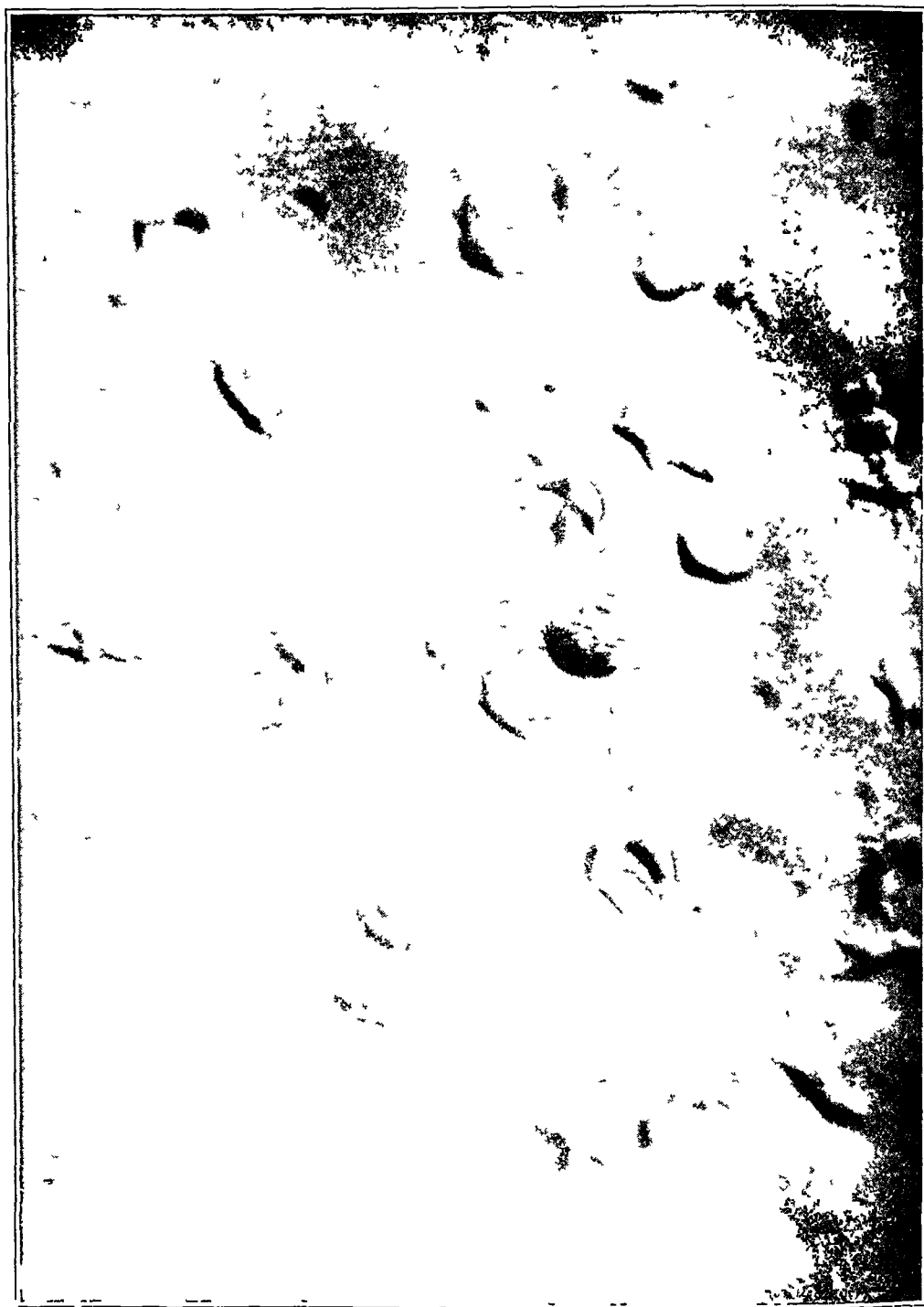


Fig 1—Photomicrograph of the sickle cells of a Mexican boy aged 9 years. The Beck and Hertz method was used, and the cells were fixed in solution of formaldehyde. Magnification, 1,000.

number included 278 children under 15 years of age and 985 adults. Of this number, 119 (9.42 per cent) were found to have erythrocytes that "sickled" when tested, as indicated in the procedure. One patient, or 0.32 per cent, of the 307 non-Negroes tested showed sickling (fig 1). In the latter group there were 189 children under 15 years and 118 adults. A complete summary of patients tested is found in table 1.

TABLE 1—*Summary of Data for Patients Tested for Sickling*

Negroes tested			
A	Negative results		
	Adults	899	
	Children	244	
	Total		1,143
B	Positive results		
	Adults	86*	
	Children	34	
	Total		120
	Total Negroes tested		1,263
	Percentage of positive results among Negroes, 9.42		
Non Negroes tested †			
A	Negative results		
	Adults	118	
	Children	188	
	Total		306
B	Positive results		
	Adults	0	
	Children	1‡	
	Total		1
	Total non Negroes tested		307
	Percentage of positive results among non Negroes, 0.32		
	Grand total of patients tested		1,570

* Includes a female showing "elliptical shaped" red blood cells (fig 2).

† Includes Nordics, Mexicans, Greeks, Italians, Spanish, Filipinos, Chinese and others (see table 3).

‡ A Mexican boy aged 10 years (fig 1). One patient other than the 1 listed here (a white male of Irish extraction) showed peculiarly shaped cells unlike any described in the literature (fig 3). Numerous subsequent tests, after the first, failed to show the same type of cells. He is, therefore, listed in the group showing negative results.

Each person whose red blood cells show the sickling phenomena is not necessarily anemic. As a matter of fact the great majority of those who showed sickling had a normal red cell count, a normal hemoglobin value, no reticulocytosis and no evidences of blood destruction at the time the blood was tested. Some authors call such a condition latent sickle cell anemia, and Cooley⁴⁷ has suggested that it be called "sicklemia," simply to indicate that the erythrocytes undergo the deformity. Only those persons who have all the signs and symptoms of

47 Cooley, T. B., and Lee, P. The Sickle Cell Phenomenon, *Am J Dis Child* 32:334 (Sept) 1926.

anemia together with the laboratory evidence, including the characteristic poikilocytosis, should be considered to have sickle cell anemia. It is generally believed, however, that every patient with "sicklemia" is potentially "anemic," although the factor that causes this regression is not definitely known. Similarly, it is believed that a person who is "anemic" may revert to the nonanemic phase.

Incidence of Sickling Reported by Previous Investigators—There is nothing in the literature whereby one may conclude from the incidence of the sickling phenomena what percentage of those in one phase of the disease may revert to the other. About all that can be assumed is that each person with sicklemia is potentially anemic and as such offers a medical problem. The incidence of those whose cells sickled, without

TABLE 2—*Comparison of Percentages of Patients with Sickling Among a Large Series of Negroes Tested by Various Investigators**

Investigators	Number of Patients Tested	Number of Positive Results	Percentage of Positive Results
Cooley and Lee ⁴⁷	400	30	7.50
Levy ⁴⁴	213	12	5.60
Graham and McCarty ¹¹	858	58	6.75
Josephs ¹²	250	16	6.40
Diggs ³⁶	827	68	8.20
Miyamoto and Korb ¹⁴ †	300	19	6.30
Present series	1,263	119†	9.42
Total	4,111	322	7.83

* Data published by investigators who have reported positive results in various communities without giving the number of persons examined or who have examined only non Negro subjects have been omitted from this table.

† These investigators have also tested non Negroes, but the data are not included in this chart.

‡ This number does not include 1 positive result for a non Negro (Mexican) and for a Negro having so called elliptical shaped cells.

regard to the presence of anemia, is shown in table 2, where the findings of previous investigators for a large series of Negroes are listed. The number of tests made (1,263) and the series of patients (119) showing sickling reported in this paper are larger than any other included in the chart. Because of the large number of tests, the results should more accurately approach the actual incidence of the sickling phenomena. As over 4,000 Negroes have been tested when the present work is included, an average incidence is determined and found to be 7.83 per cent. This percentage may, presumably, be considered as the average "sickling" expectancy for the entire Negro population in America.

Distribution of Cases Among Non-Negroes—Only three reports of a large series of tests on non-Negroes are found in the literature. Sydenstricker ⁷ found no sickling among non-Negroes in Georgia after 300 tests. Miyamoto ¹⁴ obtained similar results for 100 non-Negroes he tested in St. Louis, while Wallace ²⁶ tested 139 Mexican children and

100 Mexican adults, with 3 positive results. The 3 patients who showed sickling were all children of the same family. Lawrence⁴⁸ has reported 3 positive results for 102 non-Negroes tested, but the pictures he presented of the blood cells in his article have been criticized as not being "sickle cells" but "elliptical cells," and he has since reported them as of that type. Many isolated reports of sickling of the erythrocytes in

TABLE 3—*Nationalities of Patients Tested*¹

	No. of Patients
Born in the United States	
Negro	1,263
Non Negro	145
Foreign born	
Austria	7
Bohemia	2
Canada	3
China	3
Czechoslovakia	6
England	3
Finland	1
France	1
Germany	17
Greece	2
Hungary	4
Ireland	10
Italy	30
Jugo Slavia	4
Lithuania	15
Mexico	12
Persia	1
Philippine Islands	2
Poland	19
Rumania	1
Russia	12
Scotland	1
Spain	1
Sweden	2
Switzerland	2
Wales	1
Total	162
Grand total	1,570

* In the case of children the nationality is taken as that of the father or mother when either was born outside the United States and that of the father when both were born outside the United States.

Jews, Americans and Italians have appeared in the literature since Cooley¹⁸ reported sickling in a Greek child. Since Cooley⁴⁹ has expressed the opinion that routine tests for sickle cells should be made not only for Negroes but also for those of Mediterranean ancestry as well, the nationalities of the 307 non-Negroes reported on in this paper are shown in table 3.

⁴⁸ Lawrence, J. S. Elliptical and Sickle-Shaped Erythrocytes in Circulating Blood of White Persons, *J. Clin. Investigation* 5:31 (Dec.) 1927.

⁴⁹ Cooley, T. B., in Brennemann, J. *Practice of Pediatrics*, Hagerstown, Md., W. F. Prior Company, Inc., 1936, vol. 3, chap. 16, p. 37.

BIZARRE FORMS ENCOUNTERED

In the course of the testing of those patients whose cells sickled, 2 persons were found whose cells were bizarre and yet could not be considered sickle cells. The first patient, who had "elliptical-shaped cells" (fig 2), was a 65 year old, very dark Negro woman, a member of a family of 9, none of whom lived in Chicago and who were therefore not tested. Patients having similar blood findings have been reported by Dresbach,⁵⁰ Hunter,⁵¹ Lawrence⁵² and Terry⁵³. Terry has

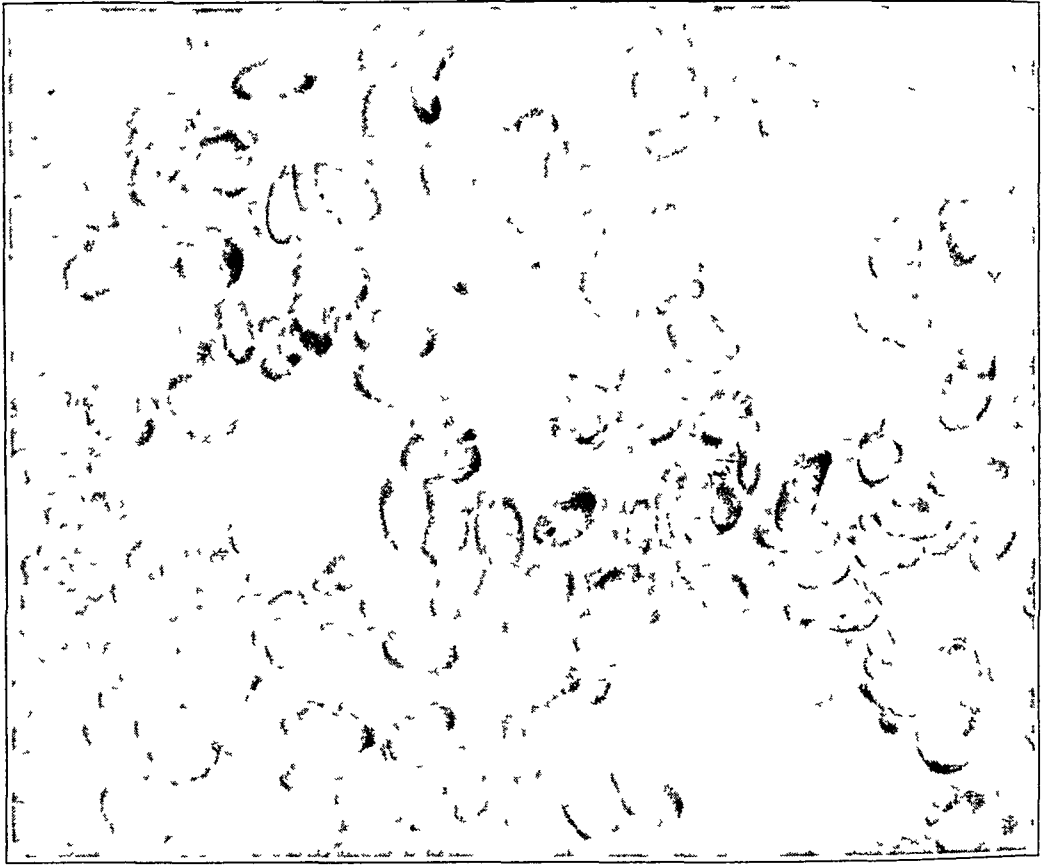


Fig 2—Photomicrograph of "elliptic" cells of a 65 year old Negress. The cells are shown to demonstrate the contrast between those in figures 1 and 3. Magnification, 750.

50 Dresbach, M. Elliptical Human Red Corpuscles, *Science* **19** 469, 1904, Elliptical Human Erythrocytes, *ibid* **21** 473, 1905.

51 Hunter, W. C., and Adams, R. B. Hematologic Study of Three Generations of a White Family Showing Elliptical Erythrocytes, *Ann Int Med* **2** 1162 (May) 1929, A Further Study of a White Family Showing Elliptical Erythrocytes, *ibid* **6** 775 (Dec) 1932.

52 Lawrence, J. S. Human Elliptical Erythrocytes, *Am J M Sc* **181** 240 (Feb) 1931.

53 Terry, M. C., Hollingsworth, E. W., and Eugenio, V. Elliptical Human Erythrocytes. Report of Two Cases, *Arch Path* **13** 193 (Feb) 1932.

collected reports of 52 cases and has found the patients to be equally divided between Negroes and non-Negroes and as to sex. A photograph (fig 3) of a camera lucida drawing of the peculiarly shaped cells present in the blood of the Irish boy referred to in table 1 shows the cells of the second patient. A total of 14 separate tests were made for the patient, with 2 or 3 smears each time. Twelve of these tests were checked by the Beck and Hertz method. When first tested, the patient was toxic. The diagnosis at this time was "bilateral otitis media" and "nephritis." Later there developed marked swelling of the joints with exquisite pain, and the final diagnosis was "chronic rheumatoid arthritis."



Fig 3—Photograph of a camera lucida drawing of cells of a 13 year old non-Negro of Irish extraction, referred to in table 1. Note the contrast between these cells and the typical sickle cells shown in figure 1. This drawing was made by Dr Katsujir Kato, of the University of Chicago, at table level using a no 10 ocular and an oil immersion lens.

Subsequent tests showed that the patient was less toxic, though his temperature continued to be elevated. The peculiarly shaped cells were seen when the child was first tested. Their shape was noted about fourteen hours after the cover slip preparation had been made. It was estimated that about 95 per cent of the cells had assumed the odd shape. An accurate word picture is, of course, somewhat inadequate, but the cells may be described as having a very small biconvex round center, about one-third the diameter of a normal red blood cell, densely packed with hemoglobin. At diametrically opposite points on the circumference of the center, long, fine spearlike processes protruded. The length of each of these processes was about twice the diameter of a

normal erythrocyte. They were almost totally transparent, except for a streak of hemoglobin that extended from the central mass to the pointed tip. These elongations did not bend from side to side as the cells were made to jostle against each other by slight pressure with the lens against the cover slip. The camera lucida drawing shown here (fig. 3) was made about forty-eight hours after the cells were first observed. Within about seventy-two hours a large majority of these erythrocytes had returned to the spherical form, and all had become round biconcave disks within five days. At no time did any of the cells have the characteristic sickle cell shape. All agglutinating reactions of both of these patients were normal.

Cooley⁵⁴ has considered the effect on the red blood cells of many infectious states and has presented drawings of the various shapes the cells may take. He has called these shapes "degrees of fragmentation" and has stated that he thinks the simplest explanation would be that "the toxins of the infection affect the marrow in such a way as to cause the production of defective cells which break down easily." He has stated that "fragmentation" can best be seen in moist films. Auer⁵⁵ has studied the structure and function of filaments produced by living red blood corpuscles and has given various examples of the shapes taken when red blood cells of human beings and animals are used. Oliver⁵⁶ has similarly studied the processes produced by human erythrocytes and has presented a method of staining them. The oddly shaped cells previously mentioned did not resemble those described by Cooley with respect to shape and the fact that they returned to the normal form instead of disintegrating while in the irregular form. They did, however, appear like some of the irregularly shaped erythrocytes described by Auer. Apparently no other explanation than the toxicity of the patient fits the reason for the alteration in the shape of the corpuscles. If this is the case, such a picture might be expected in other toxic states if tests were made to detect them.

DISTRIBUTION OF AGGLUTINOGENS O, A, B AND AB

With the exception of the work reported by Huck⁸ there is no information on the distribution of the blood groups of those persons whose red blood corpuscles sickle. Using the Moss classification, Huck found that the 14 patients of his series who showed sickling were distributed

⁵⁴ Cooley,⁴⁹ p. 4

⁵⁵ Auer, J. The Structure and Function of Filaments Produced by Living Red Corpuscles, *Am J M Sc* **186** 776 (Dec.) 1933

⁵⁶ Oliver, W. W. Staining the Processes (Flagella) of Human Erythrocytes, *J Infect Dis* **55** 267 (Nov-Dec.) 1934

as follows 4 in group IV (type O), 3 in group II (type A), 4 in group III (type B) and 1 in group I (type AB) One patient he was unable to include in either of these groups because of peculiar agglutinating reactions He made no comparison between the grouping of the patients and that of normal Negroes

The work reported herein includes a determination of the blood type of 1,560 persons The blood of only 10 of the patients tested for sickling was not typed The data obtained from these blood typings was divided into three main parts, each having the four known blood groups, O, A, B and AB The first part was composed of the non-Negroes whose erythrocytes did not show sickling (normal non-Negroes), those composing the second part were Negroes whose cells likewise showed no sickling (normal Negroes), the third part included

TABLE 4—*Distribution of Agglutinogens O, A, B and AB*

Type	Normal Non Negroes		Normal Negroes		Patients with Sickling*	
	Number	Percentage	Number	Percentage	Number	Percentage
O (I)	151	49.34	580	51.19	65	53.71
A (II)	97	31.69	279	24.62	32	26.44
B (III)	40	13.07	224	19.77	18	14.87
AB (IV)	18	5.88	50	4.41	6	4.95
Unknown†			10			
Total	306		1,143		121	

* Includes 1 non Negro (Mexican) of type O and 1 Negro with so called elliptical cells, type O

† These patients were tested for sickling, but no blood was obtained for typing

the Negroes and the single non-Negro whose red blood corpuscles showed the sickling phenomena The numerical and the percentage distribution of each blood type in each part is shown in table 4

Anomalous Iso-Agglutinins in Patients Showing Sickling—No difficulty was encountered in the routine typing of the blood, although Huck did find 1 patient whom he could not include in either of the four groups In collaboration with Guthrie, Huck³⁸ has reported another case, that of a patient whose cells sickled and who also showed anomalous agglutinating reactions They found that the washed red blood corpuscles of the patient belonged in group III Moss (type B) but the serum belonged in group I (type AB) To recheck these irregular results the cells and the serum of the patient were cross-matched against those of 59 persons whose blood was distributed among the four known groups The same end-results were obtained in each case The family of the patient was next investigated for similar anomalous reactions, and the chart for the family is reproduced here The original patient was C T

From this chart it will be seen that the red blood cells of the patient's mother, father and 2 sisters showed sickling. One of these sisters and a brother, whose cells were normal, had questionable blood types, like that of C T. The sister with the anomalous blood type married a man with normal red blood corpuscles of group I (type AB). From this union there were 2 boys with normal erythrocytes, 1 girl who had sickle cells but whose blood was of normal type and 1 with normal red blood cells but an anomalous blood type, like that of her mother and her aunt. These authors were able to find 13 specimens from the 142 persons tested that were agglutinated by the serum of patient C T. Each of these specimens was of type II. Guthrie and Huck did not state how many of the specimens that were agglutinated showed sickle cells or how many persons had serum that did not normally corre-

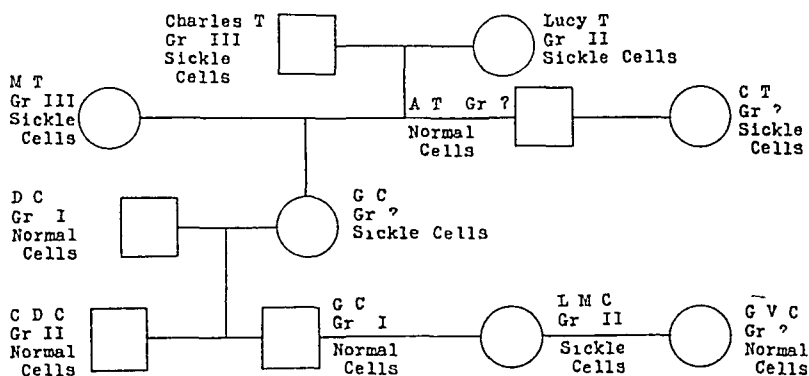


Fig 4—Chart of the family of patient C T

spond to the cell type, as was the case with their original patient. From their evidence the authors said they thought they had found a fifth isohemo-agglutinin to add to the four already known.

Since the anomalous agglutinins found by Guthrie and Huck were in blood containing sickle cells, the possibility of similar irregular reactions was considered in the series reported in this paper. Accordingly, 440 cross-matchings were made, washed cells and inactivated serum of patients with known sickle cells and the washed cells and inactivated serum of normal Negroes and of non-Negroes being used. The results are shown in tables 5 to 8. No reactions of any kind resembling those reported by Huck and Guthrie were found. In fact, all the reactions were those normally to be expected when fresh cells and serums are used. The one irregularity noted occurred when the cells were preserved⁵⁷ too long in the refrigerator.

⁵⁷ Rous, P, and Turner, J R. The Preservation of Living Red Blood Cells in Vitro, *J Exper Med* **23** 219 (Feb) 1916.

DISTRIBUTION OF AGGLUTINOGENS M, N AND MN

In 1901 Landsteiner⁵⁸ definitely proved the theory he had presented the year before that the blood of the human race can be divided into three separate and distinct groups. The fourth group was discovered a year later by von Decastello and others⁵⁹. This division of human

TABLE 5—*Cross-Matching of Washed Sickle Cells Against Inactivated Serum of Patients Showing Sickling*

Sickle Cells	Type	Sickle Cell Serum							
		S 33 Type O	S 749 Type O	S 759 Type A	S 872 Type AB	S 979 Type B	S 981 Type A	S 1020 Type O	S 1057 Type A
S 33	O	—	—	—	—	—	—	—	—
S 749	O	—	—	—	—	—	—	—	—
S 759	A	+	+	—	—	+	—	+	—
S 872	AB	+	+	+	—	+	+	+	+
S 979	B	+	+	+	—	+	+	+	+
S 981	A	+	+	—	—	—	—	+	—
S 1020	O	—	—	—	—	—	—	—	—
S 1053*	A	+	+	—	—	+	—	+	—
S 1054*	O	—	—	—	—	—	—	—	—
S 1055*	O	—	—	—	—	—	—	—	—
S 1056*	A	+	+	—	—	+	—	+	—
S 1057*	A	+	+	—	—	+	—	+	—
S 385	O	—	—	—	—	—	—	—	—

* These patients were all members of the same family. S 1053 was the mother.

TABLE 6—*Cross-Matching of Normal Washed Red Blood Cells of Non-Negroes and Negroes Against Inactivated Sickle Cell Serum*

Cells	Type	Sickle Cell Serum												
		33 O	749 O	759 A	872 AB	877 B	878 AB	979 B	981 A	1020 O	263 O	691 B	110 A	1018 O
N 860	O			—		—	—				—	—		.
N 950	A	+		—		+	—				+	+		
N 858	B	+		+		—			+	+	+		+	
N 953	O	—			—		—		—	—	—	—	+	—
N 938	A	+			—		+	—	+		+	—	—	+
N 952	A	+			—		+	—	+		+	—	—	+
N 1017	A	+			—		+	—	+		+	—	—	+
W 4	O	—	—		—		—	—	—	—		+	—	+
W 8	O	—	—		—		—	—	—	—				—
W 21	O	—	—		—		—	—	—	—				—
W 26	B	+	+		—		—	+	+	—				+
W 27	B	+	+		—		—	+	+	—				+
W 30	A	—	+		—		+	—	+	—				+
W 32	B	+	+		—		—	+	+	—				+
W 34	O	—	—		—		—	—	—	—				—
N 948	O	—			—		—	—	—	—	—	—	—	—

* N refers to cells of Negro patients, W refers to cells of non Negro patients.

bloods into the four now well known groups was based on properties found in the cells (agglutinogens) and a corresponding factor in the

⁵⁸ Landsteiner, K. Ueber Agglutinationserscheinungen normalen menschlichen Blutes, Wien klin Wchnschr **14** 1132, 1901.

⁵⁹ von Decastello, A, and others. Ueber die Isoagglutine im Serum gesunder und kranker Menschen, Munchen med Wchnschr **49** 1090, 1902.

serum (agglutinin) Since the announcement of this first discovery, Landsteiner⁴¹ has shown that by means of an immune serum from rabbits, produced by the injection into these animals of human cells,

TABLE 7—*Cross-Matching of Washed Sickie Cells Against Inactivated Serums of Normal Negroes*

Sickle Cells	Type	Normal Serums of Negroes							
		N 860 Type O	N 950 Type A	N 858 Type B	N 880 Type AB	N 938 Type A	N 948 Type O	N 953 Type O	N 1017 Type A
S 33	O	—	—	—	—	—	—	—	—
S 263	O	—	—	—	—	—	—	—	—
S 385	O	—	—	—	—	—	—	—	—
S 691	B	+	+	—	—	+	+	+	—
S 749	O	—	—	—	—	—	—	—	—
S 759	A	+	—	+	—	—	+	+	—
S 872	AB	+	+	+	—	+	+	+	+
S 877	B	+	+	—*	—	+	+	+	—
S 878	AB	+	+	+	—	+	+	+	—
S 979	B	+	+	—	—	+	+	+	+
S 981	A	+	—	+	—	—	+	+	—
S 1018	O	—	—	—	—	—	—	—	—
S 1020	O	—	—	—	—	—	—	—	—
S 1053†	A	—	—	+	—	—	+	—	—
S 1054†	O	—	—	—	—	—	—	—	—
S 1055†	O	—	—	—	—	—	—	—	—
S 1056†	A	—	—	+	—	—	+	—	—
S 1057‡	A	—	—	+	—	—	+	—	—

* After being preserved for one month these same cells when tested against the same serum were agglutinated. The cells reacted similarly against type III (B) commercial serum.

† After being preserved for one month these same cells when tested against the same serum failed to agglutinate. No agglutination occurred with type III (B) commercial serum, there was agglutination with type II (A) serum.

‡ The same family noted in table 5.

TABLE 8—*Cross-Matching of Washed Sickie Cells Against Inactivated Serums of Normal Non-Negroes*

Sickle Cells	Type	Normal Serums of Non Negroes						
		W 2 Type B	W 8 Type O	W 10 Type B	W 25 Type O	W 26 Type B	W 27 Type B	W 30 Type A
S 33	O	—	—	—	—	—	—	—
S 385	O	—	—	—	—	—	—	—
S 749	O	—	±*	±*	—	—	±*	—
S 759	A	+	+	+	+	+	+	—
S 878	AB	—†	—	—†	—	—†	—†	—†
S 979	B	—	+	—	+	—	—	+
S 981	A	+	+	+	+	+	+	—
S 1018	O	—	—	—	—	—	—	—
S 1020	O	—	—	—	—	—	—	—
S 1053†	A	+	+	+	+	+	+	—
S 1054†	O	—	—	—	—	—	—	—
S 1055†	O	—	—	—	—	—	—	—
S 1056†	A	+	+	+	+	+	+	—
S 1057‡	A	+	+	+	+	+	+	—
S 872	AB	+	+	+	+	+	+	+

* These cells had been kept in a preservative for one month when tested. When rechecked with fresh cells, all the reactions were normal.

† See note for same cells in table 7.

‡ Same family noted in table 5.

he could demonstrate even other agglutinable properties in erythrocytes for which there were no normal corresponding agglutinins in human serum. These new agglutinogens have been designated M, N and MN. Landsteiner has produced evidence to show that these factors are

inheritable mendelian dominants, and he has discussed a theory according to which the inheritance of the new agglutinogens depends on a single pair of allelomorphic genes. He⁴³ has shown further that another immune agglutinin, in addition to those mentioned, is present in the cells of Negroes, and he has stated the belief that this property, which he has called agglutinin P, is specific for that race. He suspects that with proper technic even other agglutinogens may be demonstrated in red blood cells. No application of the principle of the immune agglutinogens to the erythrocytes having the sickling trait has thus far been reported.

Using the technic outlined by Landsteiner, with the substitution of the centrifugation method for testing described by Wiener, previously mentioned in the procedure, specimens of the blood of 306 normal non-Negroes, 209 normal Negroes and 63 patients with positive sickle cells

TABLE 9—*Distribution of Agglutinogens M, N and MN*

Type	Normal Non Negroes		Normal Negroes		Positive Results*	
	Number	Percentage	Number	Percentage	Number	Percentage
M	97	31.69	61	29.18	20	31.74
N	64	20.91	56	26.79	16	25.39
MN	145	47.38	92	44.01	27	42.85
Total	306		209		63	

* Includes 1 non Negro (Mexican), type MN, and 1 Negro showing so called elliptical cells, type MN.

were typed with anti-M and anti-N immune serums. The numerical and percentage distributions of M, N and MN for each of these three groups are shown in table 9.

On examination of table 9, no striking differences in the percentage distribution of either of the three combinations of agglutinogens is noted in any of the three groups of persons studied. The percentage distribution of agglutinin N is somewhat higher among the normal Negroes and the group showing sickling, but whether this variation is significant racially needs further statistical verification.

ATTEMPT TO DETERMINE A SPECIFIC AGGLUTININ

Since no significant percentage variation was obtained when testing for M and N, a further effort was made to detect anomalous immune agglutinogens. Three immune serums, AM, ON and ABMN, produced from the blood of patients with sickle cells (2 were anemic and in the hospital at the time the blood was drawn for injection into rabbits) were separately absorbed with washed cells from white patients having the same blood type (normal and immune types). To eliminate as far as possible the blood of persons having possible intermixture

with whites, only the blood of very dark-skinned Negroes was chosen to produce the serum. The completely absorbed serum was tested against the cell suspension of 30 specimens of blood of unknown type and from patients of both races collected fresh that day. No agglutination of any of these cells or of any of the control cells occurred. The same procedure was repeated on two other occasions, fresh suspensions of unknown cells being used. No agglutination of the completely absorbed serum has ever occurred. To detect further any specific immune property possibly present in the prepared serum, each specimen was tested against the cells of 12 patients who showed various types of sickling. These cells had been kept in a refrigerator suspended in the preservative already referred to but had been washed before using. Again, no agglutination occurred with the control cells or the sickle cells. From these results it is apparent that with the methods used no specific immune agglutinin was produced in the rabbit serum with the particular sickle cells used. It should be noted, however, that at the time of the injection the cells were not actually "sickled," since none of the cells having the deformity will remain that way when exposed to air.

FACTORS IN THE SICKLING PHENOMENA

With so many specimens of blood available from persons whose cells were known to sickle, some attempt was made to study the question: Would these cells undergo their characteristic deformity in the absence of serum? For, as has been shown, Huck and Hahn individually presented evidence that serum was not needed, while Sydenstricker and Josephs have, separately, taken the opposite view. On the publication by Beck and Hertz² of a new procedure for testing for sickle cells, an excellent method was available whereby this theory could be studied. This method consists, to repeat briefly, of a saline-citrate suspension of the suspected cells overlaid with liquid petrolatum. After from twelve to twenty-four hours the cells are fixed in whatever form they may have assumed with neutral solution of formaldehyde and then examined microscopically. With this new technic four different experiments were devised for investigating the problem.

The first attempt at investigating was divided into two parts. Part one consisted of a repetition of the work of the aforementioned four authors on freshly drawn and washed cells with and without serum. By using the Beck and Hertz technic it was found that sickling of the cells occurred in approximately the same percentage in the tube containing no serum as it did in the tube having serum. Since it has not been specifically shown that only freshly drawn and washed cells must be used, it was decided that the second part of this phase of the study should be the inclusion of preserved cells of patients known

to show sickling, with the same technic as before. The results here paralleled the previous ones—sickling occurred just as well in the tube with serum as in the one without it. Care had been taken to determine whether the preserved cells had sickled while standing in the refrigerator. These results are shown in table 10. The percentages given in this chart for the two types of cells were determined by microscopic study of stained smears of the fixed cells.

By substituting plasma from normal Negroes for the serum in the foregoing test, the second test of the theory of these investigators was

TABLE 10—*Test 1 Effect of Sickling Phenomena of Fresh and Preserved Sickie Cells With and Without Sickie Cell Serum (Inactivated)**

		Washed Sickie Cells†															
		Part 1								Part 2							
		S 1018 Type O		S 1020 Type O		S 979 Type B		S 981 Type A		S 749 Type O		S 872 Type AB		S 691 Type B		S 33 Type O	
		B & H Solution Only, Control	0.1 Cc of Serum and B & H Solution	B & H Solution Only, Control	0.1 Cc of Serum and B & H Solution	B & H Solution Only, Control	0.1 Cc of Serum and B & H Solution	B & H Solution Only, Control	0.1 Cc of Serum and B & H Solution	B & H Solution Only, Control	0.1 Cc of Serum and B & H Solution	B & H Solution Only, Control	0.1 Cc of Serum and B & H Solution	B & H Solution Only, Control	0.1 Cc of Serum and B & H Solution	B & H Solution Only, Control	0.1 Cc of Serum and B & H Solution
Sickle and bizarre forms, percentage		73	77	93	90	52	64	17	19	3	11	35	46	6	9	44	59
Round and crenated forms, percentage		27	23	7	10	48	36	83	81	97	89	65	60	94	91	56	41

* The solution used by Beck and Hertz consists of equal parts of physiologic solution of sodium chloride plus 3 per cent solution of sodium citrate at pH 6.9. For the controls, the Beck and Hertz solution plus washed sickie cells was used.

† For S 1018 and S 1020 the cells were freshly drawn and washed in saline solution. For S 979 and S 981 the cells were kept in Locke's solution in the icebox for two weeks and washed in saline solution before being used. For S 749 the cells were kept in Locke's solution in the icebox for one month and washed in saline solution before being used. For S 872, S 691 and S 33 the cells were kept in Locke's solution in the icebox for seven weeks and washed in saline solution before being used.

made. As in the previous test, sickling occurred in the tube without plasma as well as in the one with it. Similar results were obtained with the third test when serum from normal white patients was used in place of the plasma. The characteristic poikilocytosis occurred in each tube. These results are shown in tables 11 and 12.

No chart is presented for the fourth test, since in each instance (control and testing tube) no sickling occurred when inactivated serum from patients who showed sickle cells was added to the saline-citrate suspension of cells from normal non-Negroes and Negroes.

Each of these tests shows that red blood cells having the sickling trait do not require the presence of either serum or plasma to assume their characteristic form. Further, test 1 (table 10) shows that whatever the factor may be that causes the cell to sickle, it remains within

the cell and under appropriate circumstances will exert itself as long as the cell remains intact This last observation, as far as is known, is not reported in previous literature

Agglutination and the Sickling Phenomena—The tests just presented have suggested another study that might be undertaken Would cells having the sickling tendency undergo this deformity after they had been agglutinated? With a fresh suspension of red blood cells of a patient with known sickling, type A-M, anti-A commercial serum was added to agglutinate the cells in a small test tube The mixture of serum and cells was allowed to stand fifteen minutes to be sure that agglutination had occurred As a control, a drop of the mixture was watched microscopically for clumping When agglutination was

TABLE 11—*Test 2 Effect of Plasma from Normal Negro Patients on Sickling Phenomena of Washed Sickie Cells*

	Washed Sickie Cells									
	S 979 Type B		S 1018 Type O		S 1020 Type O		S 749 Type O		S 872 Type AB	
	B & H Solution Only, Control		B & H Solution Only, Control		B & H Solution Only, Control		B & H Solution Only, Control		B & H Solution Only	
	0.1 Cc of Serum and B & H Solution		0.1 Cc of Serum and B & H Solution		0.1 Cc of Serum and B & H Solution		0.1 Cc of Serum and B & H Solution		0.1 Cc of Serum and B & H Solution	
Sickled and bizarre forms	+++	+++	++++	+++	+++	+++	++	+	++++	++++
Round and cre- nated forms	Few	Few	Few	Few	Few	Few	Mod- erate	Many	Few	Few

* 1 plus indicates an estimated 25 per cent, 2 plus, 50 per cent, 3 plus, 75 per cent, and 4 plus, 100 per cent The ages of the cells and the description of the controls were the same as given in table 10

definite the cell suspension in the tube was overlaid with liquid petrolatum and permitted to stand over night In accordance with the Beck and Hertz technic, these cells were examined the next morning, and it was found that sickling had occurred just as well in the tube containing the agglutinating serum as in the control tube having no serum Most of the cells were no longer clumped, however, those still agglutinated were also sickled The agglutinated cells on the glass slide, used as a control, were covered with a cover slip, and this was sealed with petrolatum On examination the next morning it was found that the clumps had not broken up and that not more than 1 or 2 cells had sickled No sickling was seen in the masses of agglutinated cells

This study was continued by taking a suspension of the same cells, agglutinating them as before and then washing and centrifugating the clumps of cells with six changes of the saline-citrate solution Between

each washing the cells were shaken for three minutes. After these washings the cells were no longer agglutinated, except for an occasional clump of two or three cells. This suspension was then overlaid with liquid petrolatum without the addition of serum, and examined the next morning by the same technic as in other tests. No sickling was noted at this time. The method was repeated with the addition of serum to one tube of the centrifugated cells and with another tube of similarly treated cells without added serum. In both instances of the repeated tests over 75 per cent sickling was obtained.

These results show that as a result of agglutination no apparent alteration in the sickling factor within the cell occurs. The 2 instances

TABLE 12—*Test 3 Effect of Normal Serums (Inactivated) from White Patients on Sickling Phenomena of Washed Sickle Cells*

	Washed Sickle Cells									
	S 1018 Type O		S 1020 Type O		S 979 Type B		S 749 Type O		S 872 Type AB	
	B & H Solution, Control		B & H Solution, Control		B & H Solution Control		B & H Solution, Control		B & H Solution Control	
	0.1 Cc of Serum and B & H Solution		0.1 Cc of Serum and B & H Solution		0.1 Cc of Serum and B & H Solution		0.1 Cc of Serum and B & H Solution		0.1 Cc of Serum and B & H Solution	
Sickled and bizarre forms, percentage	75	50	75	75	50	50	50	50	90	50
Round or crenated forms, percentage	25	50	25	25	50	50	50	50	10	10

* The ages of the cells and the description of the controls are given in table 10. The percentages are approximations.

in which no sickling occurred—that of the slide preparation and that of the centrifugated cells—can conceivably be overlooked in view of the positive results obtained in the other instances in which there was complete control.

AGE, SEX AND RACE MIXTURE OF PATIENTS SHOWING SICKLING

Most reviews of the literature on sickle cell anemia summarize the age, sex, signs and symptoms and other data as they have been presented in the reports of persons having the disease. In most instances the reports are made only for patients who are definitely anemic. Anderson⁵ has reviewed the literature with regard to these aspects and has graphically shown the age incidence and the frequency of the various signs and symptoms as they were reported for 49 patients with active anemia. Little information is obtainable for that group of patients commonly referred to as showing "latent sickle cell" anemia or "sicklemia."

Since the patients of this series who showed sickling were those in the active and the latent phase of the disease and since the group is probably the largest on record, a brief analysis seemed appropriate. An analysis in great detail was too formidable an undertaking, if not impossible, since almost all the patients were ambulatory and temporary hospitalization for study was prohibitive. The analysis was therefore confined to age, sex, race mixture (as estimated by objective inspection of the patient), blood and whatever clinical data were available. With the clinical data, roentgen studies and blood counts were included when made.

The age incidence of this series of patients showing sickling has been divided into ten year periods (table 13). Excluding those patients whose ages were not known, there were 62 persons under 30 years of age and 52 who were 30 years of age and over. As to the sex, 69.1 per

TABLE 13—*Age Incidence*

Age	Number of Patients
Less than 1 year	2
1 to 9 years	19
10 to 19 years	22
20 to 29 years	19
30 to 39 years	22
40 to 49 years	15
50 to 59 years	11
60 to 69 years	4
Unknown	6
Total	120

cent were females and 30.8 per cent males. By determining the race mixture purely on the basis of color rather than type of hair, type of features and other anthropologic standards, the series consisted of 44 black persons, 60 mulattoes, 5 quadroons and 1 octoroon. Serologic determinations were performed in the hospital laboratory, and the results given here were from the first Wassermann test of the blood made for the patient. Eleven patients (9 per cent) had no records as to the Wassermann tests. Of the remaining 111 patients, 11.1 per cent showed positive results, ranging from 1 to 4 plus, while 1.8 per cent (2 patients) showed a plus-minus, or doubtful, result. Several authors⁶⁰ have reported roentgenographic changes in the bones of children found to have sickle cell anemia. For 17 of the children in this series lateral roentgenograms of the skull and long bones were made. In no instance was any bony change detected. Fifty patients of the series had at least 1 red blood cell count, a white blood cell count, a determination of the hemoglobin value (Sahl) and a reticulocyte count. To avoid unduly lengthening this report, only the erythrocyte counts and the hemoglobin values are presented. The average red

60 Moore³⁰ Vogt and Diamond³¹ Brandau³² de Castro³³ Grinnan³⁴

cell count was 4,200,000, and the average hemoglobin value was 86.4 per cent. Twelve of the 50 patients had counts of less than 3,000,000, and 4 had counts above 5,000,000. Clinically it appears that those patients whose erythrocytes have the sickling trait are subject to all varieties of complaints and, from the diagnostic standpoint, the same maladies commonly found among a large general clinic clientele and show no evidence of a relation of any given complaint to the sickling trait.

REPORT OF CASES

Two reports of cases are presented because of their clinical interest, in that in the adult patient active anemia was present when he was 56 years of age, and the boy with sickle cell anemia became actively anemic and then reverted to the former nonanemic phase. This boy was the only patient of the series who had a palpable spleen.

CASE 1—N. P., a Negro aged 56, came to the hospital on Oct. 29, 1935, with the complaint of weakness, severe headache in the frontal region, shortness of breath on exertion, precordial pain and occasional swelling of the ankles. I had previously tested him in the clinic and found marked sickling of the red blood cells. The erythrocyte count was 1,830,000, the hemoglobin value, 30 per cent (Sahli), the white blood cell count, 6,050, and the reticulocyte count, 1.4 per cent.

Past History—The patient was born in Mississippi and moved to Buffalo, while a young man. During 1932 he was treated in the Buffalo General Hospital for "pernicious anemia" and was given liver. He has been living in Chicago for the past two years. In February 1935 he was treated at the Cook County Hospital for "partial stricture of the urethra," and after discharge he was referred to the outpatient department of Provident Hospital.

Physical Examination—Examination revealed a very dark, emaciated man who was apparently ill. There was no evidence of icterus anywhere, and the mucous membranes were markedly pale. The spleen, liver and lymphatic glands were not palpable. There was a soft systolic murmur at the base of the heart. The blood pressure was 110 systolic and 60 diastolic. There was no cardiac enlargement.

Laboratory Examination—When the patient was admitted to the hospital, six days after the first blood count had been made, the erythrocyte count was 1,860,000, the hemoglobin value, 40 per cent (Sahli), and the white blood cell count, 6,650. A roentgenogram of the chest was normal. The urine was normal except for a slight trace of urobilin. The van den Bergh test gave a delayed positive reaction, and the Wassermann reaction was negative.

Course—The patient did not show fever at any time. His appetite was always good. For the first week no medication or treatment of any kind was given. At the end of this time, the red blood cell count was 2,930,000, the hemoglobin value, 55 per cent (Sahli), and the white blood cell count, 7,250. From November 12 to December 6 the patient was given 2 cc of hog liver extract intramuscularly twice weekly. Complete blood counts were made twenty-four hours after each injection. At the end of this course of treatment, during which he was given 16 cc of the extract, the erythrocyte count was 3,100,000, the white blood cell count, 5,900, the hemoglobin value, 65 per cent (Sahli), and the reticulocyte

count, 24 per cent. The patient was then discharged. He had gained 2 pounds (1 Kg), felt well and looked much improved. He has been seen regularly each week in the clinic, at which time complete blood counts have been made. On May 27, 1936, six months after his discharge, the erythrocyte count was 3,350,000, the hemoglobin value, 85 per cent (Sahli), and the white blood cell count, 3,650. Sickling continued at from 90 to 95 per cent.

CASE 2—R F, a 3 year old mulatto boy, came to Provident Hospital on April 13, 1936 (for the third time since his birth there) because of a cold and



Fig 5—A, a 3 year old boy, R F, case S 1057. When admitted to the hospital, this patient had an erythrocyte count of 1,780,000 and a hemoglobin value of 50 per cent (Sahli). Note the outline of the spleen. B, a 4 year old girl, J C, case CS 270. The erythrocyte count was 3,200,000, and the hemoglobin value was 82 per cent (Sahli). Compare the color of this "creole" girl (French-Spanish-Negro blood) with that of the Negro boy (A).

cough, pain in the upper left portion of the abdomen and constipation. He had previously been tested in the clinic for sickling, and it was found that almost complete sickling occurred in six hours.

Past History—The patient was born in Provident Hospital, with a birth weight of 8 pounds and 7 ounces (3,860 Gm). He was breast fed until he was 8 months of age, when he was again admitted to the hospital, presenting a large

inguinal hernia on the left, which could not be controlled with a truss. He was operated on, and convalescence was normal. The erythrocyte counts at that time were 5,000,000 and 4,900,000, with 10,000 and 8,400 white blood cells and hemoglobin values of 85 and 80 per cent (Tallqvist). Since birth the child had been brought to the clinic frequently because of infections of the upper respiratory tract of varying severity. He was again admitted to the hospital, on June 21, 1935, when 2 years of age, with massive pneumonia involving the upper and

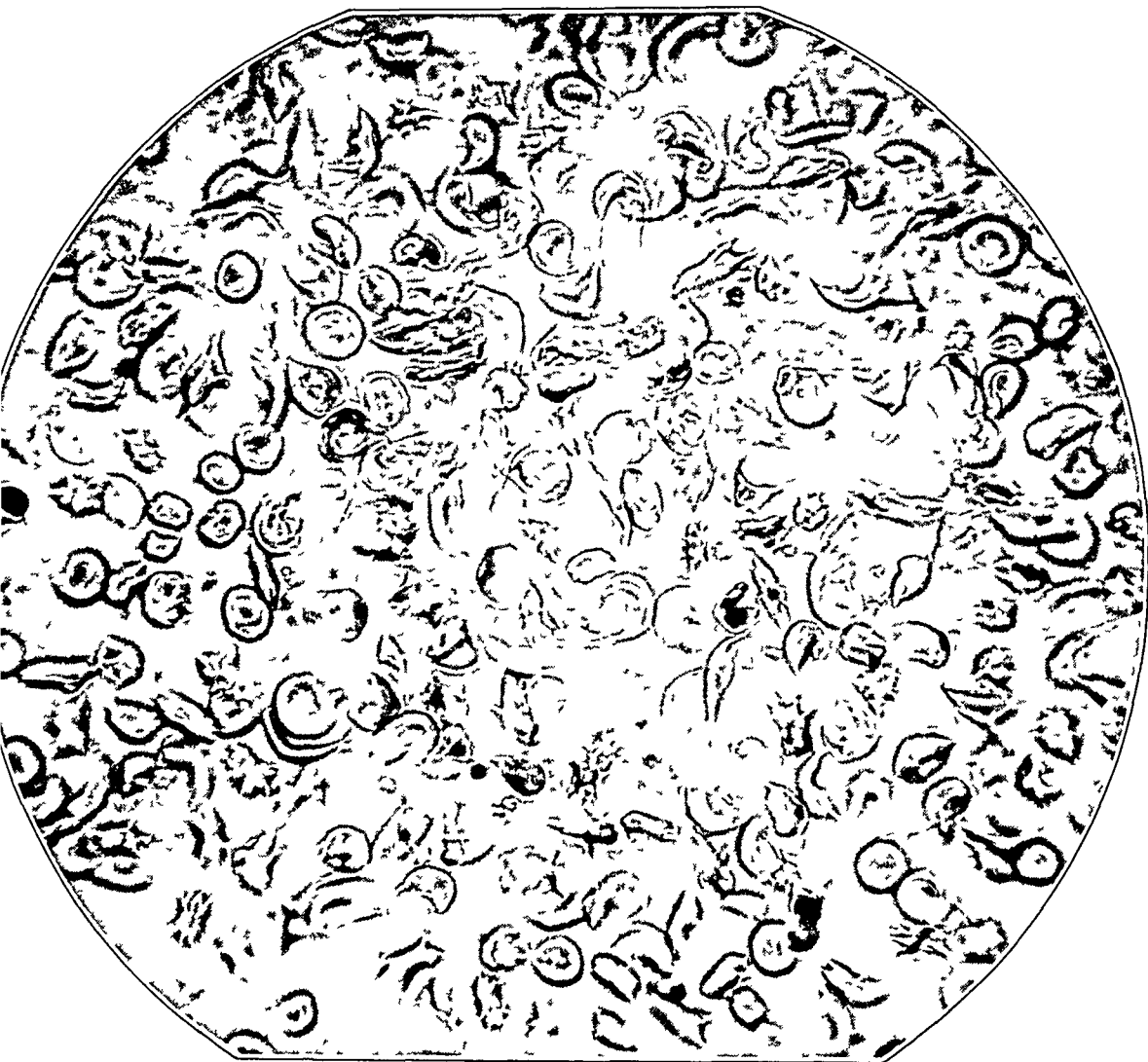


Fig 6—Photomicrograph of the sickle cells in case S 1057 (fig 5 A). The "cover slip method" was used. Magnification, 750.

middle lobes of the right lung. Blood counts showed 3,500,000 and 3,950,000 erythrocytes, 20,300 and 8,000 leukocytes and 60 and 75 per cent hemoglobin (Sahli).

Family History—The father and mother were living and well. The mother, 2 brothers and 1 sister showed sickling of the red blood cells but had no anemia. One brother and 1 sister did not show sickling. The father refused to come to the hospital for tests. There was no history of tuberculosis, syphilis, epilepsy or miscarriages.

Physical Examination—The patient weighed 27 pounds (12 Kg) when admitted. The nutritional state was fair. He did not appear ill. There was a profuse mucopurulent nasal discharge. There was no icterus, but the skin had a peculiar mustard-like color. The mucous membranes were markedly pale. The lymphatic glands were easily palpable in the cervical and the axillary regions. There were coarse moist rales in both lungs anteriorly and posteriorly. No dulness was noted on percussion. There were no cardiac murmurs. The spleen was palpable 1 cm below the costal margin. There was no abdominal tenderness. The temperature was 98.6 F.

Laboratory Examination—The blood count showed erythrocytes, 1,780,000, hemoglobin, 50 per cent, white blood cells, 8,000, and reticulocytes 8.8 per cent. The differential count was 38 per cent polymorphonuclears, 60 per cent lymphocytes and 2 per cent monocytes. The urine was normal except for the marked presence of urobilin. The Mantoux reaction (1:10,000) was negative. Roentgenograms of the chest, long bones and skull were all normal. The icteric index was 12. There was a delayed direct van den Bergh reaction, and the Wassermann reaction was negative. Including the first count, 20 complete blood counts were made for this patient. Sternal bone marrow was studied by Dr. K. Kato, of the University of Chicago, who reported it as showing "generalized hyperplasia of all the bone-marrow elements but without an increase in any one element."

Treatment—From April 14 to May 29, 1936, the patient was given 1 teaspoonful three times a day of a malt preparation containing 64 grains to the ounce (13 per cent) of iron and ammonium citrates. Blood counts were made twice weekly during this interval. At one time the blood count showed erythrocytes, 3,070,000, hemoglobin, 65 per cent (Sahli), white blood cells, 11,850, reticulocytes, 8.8 per cent, and eosinophils, 9 per cent. But at the end of the course of iron a blood count showed erythrocytes, 2,220,000, hemoglobin, 55 per cent, white blood cells, 12,950, and reticulocytes, 22.1 per cent, with 8 normoblasts seen among 200 cells. The patient was then given 1 cc intramuscularly of hog liver extract at two day intervals for four injections. Blood studies were made between injections. The patient resisted these injections strenuously. After the liver extract was stopped, the red blood count showed erythrocytes 2,180,000, hemoglobin, 62 per cent, white blood cells, 16,950, and reticulocytes, 21.8 per cent. He was then given 2 teaspoonfuls of a commercial liver, iron and copper preparation before each meal. On June 19, when the patient was discharged, he had the same red blood cell count and hemoglobin value, but the white blood cell count had dropped to 9,100 and the reticulocyte value to 15.5 per cent.

Course—The patient had a continuous low grade fever most of the time, and there was an occasional rise to 102 F. The infection of the upper respiratory tract was slow in clearing up. The white blood cell counts given here were high when the temperature was elevated. On discharge he had gained 1½ pounds (680 Gm). While he was in the hospital the spleen enlarged to 4 cm below the costal margin but gradually decreased until it was 1 cm below the costal margin on discharge. There was no urobilin, his color had improved, the lungs were clear and the patient was active. During the summer he was taken to the country.

The patient was again admitted to the hospital, on October 19, because of a severe infection of the upper respiratory tract and abdominal pain. The blood count showed erythrocytes, 2,000,000, leukocytes, 8,450, hemoglobin, 50 per cent (Sahli), and reticulocytes, 4.6 per cent. The spleen was still palpable about 1

inch (2.5 cm) below the costal margin. The preparation of iron and ammonium citrates was used as before, plus 1 cc of liver extract intramuscularly three times weekly. The patient remained in the hospital until November 12, when the blood count showed 3,240,000 erythrocytes, 10,000 leukocytes and 60 per cent (Sahli) hemoglobin. Since the patient's family is of low intelligence, he will undoubtedly return again with infections of the upper respiratory tract and perhaps severe anemia.

COMMENT

While the incidence of patients showing the sickling phenomena in this series is higher than any previously reported in the literature, as indicated in table 2, it should be noted that the number of patients tested is also larger than in any other report. The total series, however, is not entirely composed of single unrelated persons.

The inheritance of the sickling phenomena, already recognized in the literature and also shown by Huck⁸ to follow the mendelian law, is well brought out in the series presented here. Forty-one of these patients represented sixteen different family groups varying from 2 to 5 members in each. In most cases there were only 2 members of the family tested, although whenever possible an attempt was made to test all the members. In no instance were both parents tested, and in most instances the father was the least inclined or accessible for tests.

The immunologic studies show that the sickling trait is apparently not confined to persons of any one of the isohemo-agglutinin or immune agglutinogen groups of which there is knowledge at present. It may still be possible that some immune property will be found in the red blood cells having this characteristic poikilocytosis.

The anomalous agglutinins found in a patient who showed sickling and in members of her family, as reported by Huck and Guthrie³⁸ but not found in any of the patients of the series presented here, might possibly be explained by the fact that both parents of the patient showed sickling. This postulation was not mentioned by the authors.

The tests presented in the "factors in the sickling phenomena" show conclusively that whatever the factor may be, it is inherent in the cell and not in the serum. From these tests it is apparent that any future investigative attack must be made on the cell itself and not on the serum. It may be that the protein constituents of the protoplasmic structure of the cell hold the clue.

Since no patients attending the syphilis clinic were tested, the incidence of positive Wassermann reactions among the series of patients with sickling is startling, even if it is assumed that a single report is not conclusive in all cases. At least the need for routine serologic determinations and rechecks of all positive reactions is clearly indicated. Obviously, syphilis has no part in the sickling of erythrocytes.

No satisfactory conclusion as to treatment can be drawn from the 2 case reports. While improvement was shown by the first patient as far as the erythrocyte count and hemoglobin value are concerned, one cannot, using the same standards, say the same for the second patient. In each case, however, the apparent clinical improvement based on gain in weight, increased activity, lack of complaints and general appearance was evident. On this same basis improvement has been noted among other patients treated with the same malt preparation containing massive doses of iron. Since all the laboratory work reported in this paper was done by the same person, the factor of error in each instance cannot be attributed to the variability in the technic of different persons.

CONCLUSION

A total of 1,570 patients were tested for sickling of red blood cells. The group consisted of both adults and children. There were 1,263 Negroes (94.2 per cent who showed sickling) and 307 non-Negroes (0.32 per cent).

The blood type of 1,560 of the patients tested for sickling was determined by means of the standard laboratory "slide method." The percentages of each blood group in the series of patients who showed sickling was compared with similar groups among the normal Negroes and non-Negroes. In general there was no marked tendency for the patients who showed sickling to be concentrated in any one blood group.

The distribution of the immune agglutinogens M and N was determined for 306 non-Negroes, 209 normal Negroes and 63 patients who showed sickling. The distribution of these immune agglutinogens in the patients who showed sickling corresponded, within limits, to that of the normal persons of both races.

An attempt was made to detect a specific immune agglutinin for those who showed sickling. By the method used no specific agglutinin was found.

The anomalous isohemo-agglutinogens which were found by another investigator in patients who showed sickling were not found in this series by cross-matching the cells and serum of patients who were known to show sickling against the cells and serum of the normal persons of both races.

Tests confirmed the work of Huck and Hahn, in which they found that serum is unnecessary in producing the sickling phenomena.

It is shown further in the same tests that the sickling factor remains within the cell, no matter how long preserved, as long as the cell itself remains intact.

Individual analysis of the entire series of 120 patients who showed sickling was made, and reports of 2 cases are given.

This project was carried out under the direction of Dr Julian H Lewis, of the Otho S A Sprague Memorial Institute, the Department of Pathology, the University of Chicago. Technical assistance was rendered in certain phases of the work by Dr Katsujı Kato, of the University of Chicago, and many members of the staff of Provident Hospital cooperated.

Eighty-five of the Negroes and all but 5 of the non-Negroes were tested while they were in the men's medical wards and in the wards of the Children's Hospital, both of Cook County Hospital. Permission to study these patients was given by Drs I Pilot, R Jaffe and M Blatt.

NOTE—I was unaware of work by Killingsworth⁶¹ at the time this paper was compiled. The work herein described was completed in 1936.

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⁶¹ Killingsworth, W P, and Wallace, S A. Sicklemia in Southwest, South M J 29 941 (Sept) 1936.

PULSATIONS OF THE WALL OF THE CHEST

IV PULSATIONS ASSOCIATED WITH ADHESIVE PERICARDIAL DISEASE

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VIENNA, AUSTRIA

Since the time of Skoda,¹ three pulsatory findings have been considered to be essential for the diagnosis of adhesive pericardial disease. They are the systolic depression over the cardiac area, the diastolic cardiac thrust and the absence of the apical thrust.

Adhesions between the heart and the pericardium, particularly along their caudal aspect, inhibit greatly the change in shape which during systole would lead to elevation of the heart and with it to a thrust of the apical portion against the thoracic wall. Hence the apical thrust is usually absent in adhesive pericardial disease. This diagnostic finding, however, should not be evaluated too highly, because the apical thrust is often absent in the adult and, in addition to adhesive pericardial disease, there are a good number of other factors capable of diminishing or abolishing the apical thrust. Bamberger² has already pointed out and my colleagues and I have made the same observation that a hypertrophic heart may occasionally cause an apical thrust in spite of the presence of adhesive pericardial disease and that likewise a thrust may be caused by a right ventricle of a type which is characteristically present in disease of the mitral valve.

The systolic depression of the thoracic wall is considered to be the most important sign of adhesive pericardial disease, particularly if it is noted over a larger area (Sahl³) and if the ribs are included in the depression (Wenckebach⁴). One should evaluate cautiously those small localized depressions of the thoracic wall noted in the vicinity of a powerful apical thrust or taking its place when the supra-apical portion thrusts against the ribs. A systolic depression is not uncommonly found with disease of the mitral valve lateral to the area of the

Translated by Hugo Roesler, M D, Philadelphia

From the *Heizstation*, Dr Hans Horst Meyer and Dr Emil Zak, directors

1 Skoda, J. Abhandlung über Perkussion und Auskultation, ed 6, Vienna, Braumüller u Seidel, 1864

2 von Bamberger, H. Lehrbuch der Krankheiten des Herzens, Vienna, W Braumüller, 1857

3 Sahl, H. Lehrbuch der klinischen Untersuchungsmethoden, ed 6, Leipzig, F Deuticke, 1914-1920

4 Wenckebach, K F. Beobachtungen bei exsudativer und adhesiver Perikarditis, Ztschr f klin Med 71 402, 1910

forceful thrust of the right ventricle and over the area of the apical portion, this indicates an associated movement, and it is not justifiable to make a diagnosis of adhesive pericardial disease in these cases

The greater majority of authors have expressed the belief that the diffuse depression of the thoracic wall in adhesive pericardial disease cannot be explained by inner adhesions only, they have claimed that outer adhesions also are a necessary prerequisite. Skoda said he thought that an inward pull of the intercostal spaces on the left was observed only in those cases in which in addition to pericardial obliteration there was fixation of the pericardium against the costal pleura. This would cause fixation of the heart against the internal wall of the chest, and the obliteration of the left pleural sinus would prevent the free shift of the lung necessary to fill in the space made vacant during systole. If, in addition, the heart (and the pericardium) were also attached to the spine, there would be observed a retraction not only of the intercostal spaces on the left but of the lower half of the sternum. A similar point of view has been expressed by Bamberger² and Mackenzie⁵. This opinion cannot be maintained, as is evident from a study of cases in which there was a diffuse systolic depression of the thoracic wall during life while postmortem examination revealed obliteration of the pericardial cavity only. Sacconaghi⁶ has reported on such experiences, and my colleagues and I have had occasion to note similar cases.

K. J. was a woman aged 66. The clinical diagnosis in her case was *concretio et accretio cordis* (obliteration of the pericardial cavity with external adhesions). Postmortem examination led to a diagnosis of isolated *concretio* (obliteration of the pericardial cavity only). When the patient was first examined there was noted over the cardiac area a diffuse jerky pulsation, which was thought for a long time, erroneously, to be the systolic cardiac thrust. Careful correlation with the arterial pulse, however, showed that there was a diastolic propulsion of the thoracic wall which was preceded by a much less distinct systolic depression of the soft tissues and the ribs. An apical thrust was not felt. The previously mentioned pulsation was more marked on the left side in the fifth intercostal space (fig. 1A), but it was recognized also in the fourth intercostal space, and it extended caudad to the costal arch. Near the left midclavicular line there was noted a marked depression with a sagittal direction, while near to the sternum a shift in frontal direction, i. e., from left to right during systole, was more marked. Over the right side a similar pulsation was noted extending from the fifth rib caudad to the costal arch, with a mainly frontal direction. Here likewise the abrupt diastolic shift from left to right was much more impressive than the systolic shift. Simultaneously the ribs were slightly bowed during systole, while during diastole they underwent a flattening. The summation of the frontal movements of each half of the chest resulted in a definite pulsatory shift of the whole chest, which, as mentioned before, was more definite during diastole than during systole.

⁵ Mackenzie, J. *Lehrbuch der Herzkrankheiten*, German translation by C. J. Rothberger, Berlin, Julius Springer, 1923.

⁶ Sacconaghi, G. L. *Die klinische Diagnose der Herzbeutelverwachsung (Fibrosia cordis)*, Leipzig, C. Kabitzsch, 1923.

On the right side cardiac dullness could not be determined by percussion because of the presence of hydrothorax. The lower sternal portion was flat. No abnormal dullness was found in the second and third intercostal spaces to the left of the sternum. On auscultation a clear first sound at the apex, reduplication of the second sound and faint sounds at the base were noted. An electrocardiogram showed a sinus rhythm, with a heart rate of 120. The blood pressure was 120 systolic and 80 diastolic. The liver extended 3 fingerbreadths beyond the costal arch in the right midclavicular line and showed a weak double-wave pulsation.

Roentgenograms showed slight enlargement of the heart. A correct determination of the size was impossible because of hydrothorax on the right.

Postmortem examination revealed that the pericardial surface was freely accessible. The epicardium and pericardium were completely fixed and inseparable, calcareous deposits were not palpated. The heart was small. The cavities of both ventricles were small. All the valves were normal.

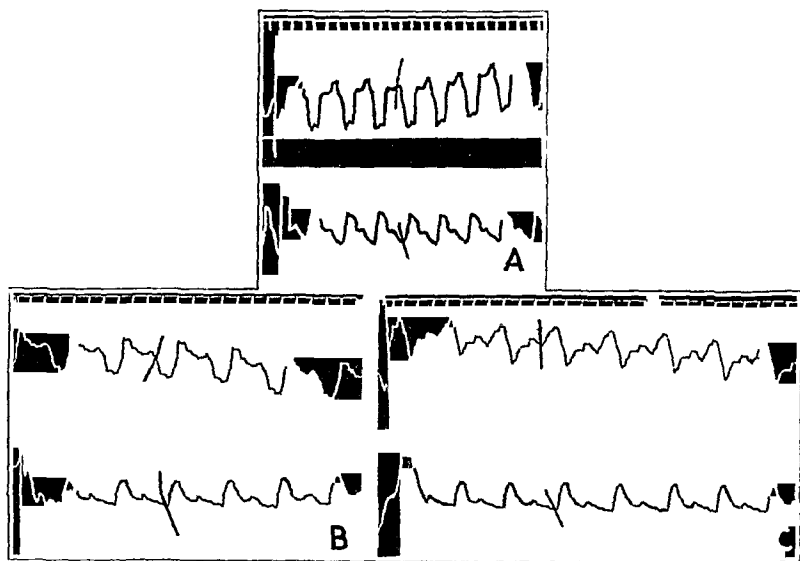


Fig 1—*A*, the graph demonstrates the systolic depression of the precordium in obliterative pericardial disease, without external adhesions (patient K J). The lower graph is for the radial artery and the upper graph for the fifth intercostal space in the left midclavicular line. The mark shows the beginning of the expulsion period. *B* and *C*, the graphs indicate the oppositely directed movement of the right and left sides of the chest, respectively, in adhesive pericardial disease (patient B F). In *B* the lower graph is for the radial artery and the upper graph for the fourth intercostal space in the left midclavicular line. In *C* the lower graph is for the radial artery and the upper graph for the fifth intercostal space in the right midclavicular line.

The postmortem examination in this case did not verify the clinical diagnosis of *acretio* (external adhesions). The heart was fixed neither to the ventral wall of the chest nor to the spine. There was noted only an obliteration of the pericardial cavity. This case demonstrates

that inner pericardial adhesions can cause a diffuse systolic depression as well as a diastolic propulsion

Under normal conditions the aspiratory action of systole on the thoracic wall is compensated for by the opposing, centrifugal forces of the change in shape, i. e., the increase in the curvature, and, particularly, the lever movement of the heart. The presence of partial adhesions between heart and pericardium on the caudal surface of the heart is sufficient to interfere with the alteration in shape, especially the systolic lifting of the apical portion. Then the most important forces disappear which counteract the aspiration due to the reduction of the ventricular volume during the systolic efflux (myocardia), and aspiration can act undisturbed on the ventral wall of the chest. Added to this is a second important factor in the development of the systolic depression of the thoracic wall in adhesive pericardial disease, i. e., a change in the mechanics of the ventricular systole. Under normal conditions about five sixths of the decrease in volume is attained by longitudinal shortening of the ventricular cone, whereas the marginal movement contributes little to the expulsion of blood (Straub⁷ and Schwarz⁸). When the pericardial cavity is obliterated, however, the longitudinal contraction of the heart is interfered with, for the pericardium is immovably attached by adhesions to the blood vessels at the base of the heart. In order to attain a sufficient stroke volume, this reduction in the longitudinal contraction is compensated for by increased marginal excursions. This agrees with the fact that in cases of distinct systolic depression of the thoracic wall roentgenologic examination often reveals remarkably large excursions of the ventricular margins.⁹ This fact must be especially emphasized, for the generally accepted idea is that in cases of adhesive pericardial disease fluoroscopy reveals abnormally small movements of the ventricular margins exclusively. Exactly the reverse can, at least in many cases, be demonstrated. The great amplitude of the cardiac silhouette reminds one, at first glance, of that seen in cases in which there is a much increased stroke volume, as in marked bradycardia. Yet in obliterative pericardial disease the small amplitude along the arterial trunks is in vivid contrast to the large amplitudes of the ventricular margins. Hence, it may be concluded that the increased pulsation of the ventricle does not express

7 Straub, H. Dynamik der Klappenfehler des linken Herzens, Verhandl. d. deutsch. Gesellsch. f. inn. Med., Kong. 41, 1929, p. 277, Die Dynamik des Herzens, in Bethe, A., and others. Handbuch der normalen und pathologischen Physiologie, Berlin, Julius Springer, 1926, vol. 7, pt. 1, pp. 235 and 241.

8 Schwarz, G. Ueber röntgenoskopische Messung und Analyse der Herzkammeraktion, Med. Klin. 16 947, 1920.

9 Dr. H. Roesler gave me this information.

an increased ventricular stroke volume but corresponds to an altered mode of ventricular contraction. The increase in the marginal amplitude leads to an increased direct aspiratory action on the ventral wall of the chest, furnishing an explanation for the forceful systolic depression, which can be seen in certain cases of adhesive pericardial disease.

Frequently, when a patient with obliterative pericardial disease is being examined the systolic depression is much less noticeable than the abrupt diastolic propulsion of the thoracic wall at the beginning of diastole. This diastolic propulsion will generally be confused with the normal systolic heart beat if one neglects to palpate the radial pulse simultaneously so as to determine the cardiac phase.

Several factors are responsible for the appearance of the diastolic cardiac thrust. Skoda said he thought that this was merely a compensation for the systolic depression of the thoracic wall, but this cannot be fully accepted, since Brauer¹⁰ has shown that the diastolic propulsion likewise may be observed after cardiolysis. Inhibition of the systolic change in the shape of the heart seems to be a decisive factor. Under normal conditions the systolic change in shape gives the heart, and thereby also the thoracic wall, a powerful thrust forward during systole, so that in the subsequent diastolic relaxation, an opposite (centripetal) movement of the heart and thoracic wall is called forth. Hence, the tendency to centrifugal movement caused by the diastolic filling of the ventricle cannot come into full play under normal conditions. But since in adhesive pericardial disease the systolic elevation of the heart is absent, the centrifugal impulse due to ventricular filling can act unrestrictedly on the thoracic wall. This is especially true in cases of congestive failure in which the blood is forced with increased momentum into the ventricles at the beginning of diastole.

Sahl said he believed that the diastolic cardiac thrust may be looked on as evidence for the presence of external adhesions, indicating that the thoracic wall is actively drawn inward from within, this would call forth the oppositely directed movement during diastole. Sahl stressed this point in view of cardiolysis, which he said he believed to be promising only if there are adhesions between the pericardium and the thoracic wall in addition to an obliteration. This opinion is erroneous in two ways. First, it makes no difference whether the heart causes a depression of the thoracic wall because of the presence of adhesions or because of an increased stroke volume, considerable contact of the enlarged heart with the thoracic wall or some other factor. In any case it has to do an increased amount of work, and the condition is relieved by resection of the adjacent stiff portions of the thoracic wall, as has been shown for the enlarged heart without pericardial adhesions by

10 Brauer, L. Untersuchungen am Herzen, Verhandl d Kong f inn Med
21 187, 1904

French authors (Worms and d'Aubigné¹¹) Also the previously mentioned observations at the bedside and at postmortem examination have shown that external adhesions are not necessary for the development of a diastolic cardiac thrust In the aforementioned case of isolated obliteration of the pericardial cavity there was a typical diastolic forward thrust which for a long time imitated a normal cardiac thrust Likewise, experiences with tricuspid regurgitation (Volhard¹² and Lang¹³), in which a diastolic cardiac thrust was reported in the absence of pericardial adhesions, made it clear that external pericardial adhesions are unnecessary for the development of these phenomena of pulsation

Skoda has shown that the systolic depression of the thoracic wall in the presence of obliteration of the pericardial cavity is directed not perpendicularly to the frontal plane but toward the sternum This movement is more marked in the area of the apical pole, while the intensity diminishes toward the sternum This is explained by the fact that in the presence of pericardial obliteration the direct aspiratory effect of the heart on the thoracic wall prevails, this is more marked in the portion near the apex The pulsatory depression on the left side calls forth an associated pulsatory movement on the right, where the ribs bulge slightly and move a little to the right The summation of both pulsations leads to a frontal shift of the whole chest from left to right during systole

A similar observation has been made in many cases of tricuspid regurgitation With this valvular lesion the pulsation on the right side is an expression of a primary direct impulse caused by the impact of blood which has regurgitated into the liver The hand placed on the thoracic wall perceives the forceful thrust The pulsation on the right side in oblitative pericardial disease is an associated movement, much weaker than the one on the left and as a rule better perceived by inspection than by palpation This is important in the differentiation of the two disease entities that are otherwise so similar As a further point of differentiation it should be mentioned that with tricuspid regurgitation the systolic shift of the chest to the right is found to be much more distinct than the opposite movement during diastole, while in oblitative pericardial disease the diastolic propulsion is usually forceful and therefore represents a more impressive pulsatory phenomenon than does the systolic depression Correspondingly, one finds

11 Worms, R, and d'Aubigne, R M Une observation de thoracéctomie pré-cordiale pour symphyse du péricarde, *Bull Soc de pédiat de Paris* **26** 219, 1928

12 Volhard, F Ueber Leberpulse und uber die Compensation der Klappenfehler, *Berl klin Wchnschr* **41** 522, 1904

13 Lang, G Ueber einige durch die Herzaktion verursachte Bewegungen der Brustwand und des Epigastriums, *Deutsches Arch f klin Med* **108** 35, 1912

in constrictive pericardial disease that the pulsatory associated movement on the right side, consisting of a shift (diastolic) to the left, is abrupt and forceful, while the systolic propulsion on the right side is much weaker and takes place almost imperceptibly. The following report is of a patient who showed the characteristic pulsations in an impressive manner. The diagnosis of adhesive pericardial disease was proved by the roentgenologic demonstration of calcareous deposits

B F was a man aged 19. A clinical diagnosis of adhesive pericardial disease was made, apparently on the basis of a tuberculous polyserositis, with moderate signs of heart failure. There was a definite bulge over the cardiac area. A diffuse pulsatory propulsion of the precordium was more marked in the fourth and fifth intercostal spaces, 2 fingerbreadths within the left midclavicular line. The first impression was of a systolic cardiac thrust. Comparison with the radial pulse showed that the propulsion took place during diastole, while there was a depression

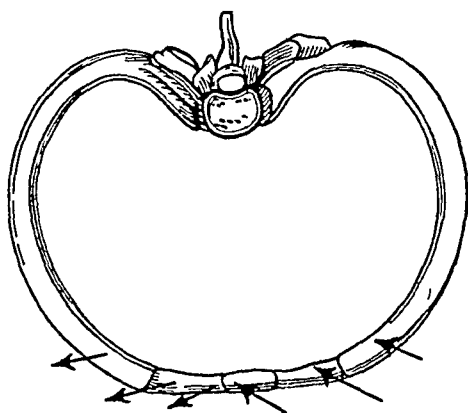


Fig 2 (patient B F) —The arrows indicate the direction of the pulsations of the thoracic wall

of the ribs and soft tissues during systole. The diastolic movement was abrupt and marked—much more impressive than the systolic depression. The latter movement comprised nearly the whole left side of the ventral wall of the chest, evidently from the second rib to the costal arch. It was more marked between the left midclavicular and the parasternal line and affected ribs as well as soft tissues (fig 1 B). The depression was not perpendicular to the frontal plane but was combined with a frontal movement directed to the right. The sagittal movement of depression prevailed over the lateral portions of the left side of the chest, while near the sternum the pulsatory component with frontal direction was more marked, the sternum itself revealed an almost pure frontal shift from left to right. The right side of the chest likewise showed a diffuse pulsation, extending from the second rib to the costal arch. As compared with that of the left side, the whole movement was much weaker, being best noted between the third and the fifth rib (fig 1 C), here the movement of sagittal direction (systolic propulsion) was overlaid by a frontal shift to the right. The summation of the frontal pulsations of both sides of the chest gave a marked systolic shift of the whole

chest from left to right (fig 2), but still more impressive was the jerky diastolic movement in the opposite direction. The pulsation at the right side over the hepatic area was much less pronounced than that in the upper portion of the chest. The liver extended 3 fingerbreadths beyond the costal arch in the right midclavicular line, and palpation revealed, in addition to a small presystolic wave, a large systolic elevation which was followed by marked diastolic collapse.

Percussion showed that the cardiac area extended 2 fingerbreadths beyond the right sternal border. The lower sternal area was flat. No abnormal dullness was found in the second and third intercostal spaces to the left of the sternum. Auscultation revealed that the first sound at the apex was moderately loud, there was reduplication of the second sound, the second part of which coincided exactly with the visible and palpable diastolic propulsion of the thoracic wall. A similar finding was noted over the base. Here the second sound was definitely split. Murmurs were not present. The rhythm was regular, and the heart rate was 88. The blood pressure was 100 systolic and 45 diastolic.

Roentgenograms showed that the cardiac silhouette was moderately enlarged to either side, the transverse diameter being 14.3 cm. There were unusually large pulsatory amplitudes along the left lower and apical borders, the latter showed a definite systolic elevation. The silhouette revealed a definite concentric movement of the cardiac borders during systole. The amplitudes along the silhouettes of the aorta and pulmonary artery were small, in contrast to the large amplitudes of the ventricular contours. Hence the marked marginal movements of the heart could not correspond to an increased stroke volume. In both oblique views calcareous deposits were noted along the surface of the silhouette.

Adhesive pericardial disease is differentiated from tricuspid regurgitation by the absence in the former of a forceful systolic hepatic regurgitation pulse. The combination of tricuspid regurgitation with adhesive pericardial disease makes the diagnosis of the latter condition extremely difficult. Since pulsatory phenomena on the left side of the chest not associated with a hepatic regurgitation pulse will be attributed first of all to tricuspid regurgitation, the detection of pericardial deposits of lime salt will be the only finding, in addition to tricuspid regurgitation, on which to base a diagnosis of adhesive pericardial disease.

SUMMARY

Diffuse pulsations of the thoracic wall in the presence of adhesive pericardial disease are by no means necessarily associated with external adhesions. Two factors play the main rôle: (1) an inhibition of the systolic change of shape of the heart whereby the aspiratory forces due to reduction of the ventricular volume during the systolic efflux prevail and (2) a change in the mechanism of volumetric diminution so that the marginal movements of the ventricles prevail because the longitudinal shortening of the ventricular cone is inhibited. Fluoroscopy in instances of oblitative pericardial disease associated with marked depression of the thoracic wall does not necessarily reveal a diminution of the marginal movements of the silhouette, as commonly accepted, but, on the contrary, rather strikingly large amplitudes may be observed.

The inhibited systolic change in the shape of the heart due to internal adhesions is of decisive importance for the appearance of a diastolic propulsion of the thoracic wall. External adhesions are not a prerequisite.

Similar to tricuspid regurgitation, adhesive pericardial disease is not rarely accompanied with a pulsatory movement of the whole chest directed from left to right during systole, this is due to a pulsatory associated movement of the right side of the chest. Tricuspid regurgitation is differentiated from adhesive pericardial disease by the absence in the latter of a forceful systolic hepatic regurgitation pulse.

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PULSATIONS OF THE WALL OF THE CHEST

V PULSATIONS ASSOCIATED WITH MITRAL REGURGITATION AND ANEURYSMAL DILATATION OF THE LEFT AURICLE

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Under normal conditions one may not expect the left auricle to transmit its movements against the thoracic wall, because it lies almost exclusively at the dorsal aspect of the heart. Also, the degree of the pulsatory amplitude is much too weak to produce visible or palpable pulsatory phenomena. In the presence of disease of the mitral valve the left auricle may dilate exclusively dorsad and occasionally to the right side of the chest (Stoerk¹). An anterior roentgenogram will reveal that the left auricle overlaps the right auricle on the right side, resulting in a subdivision of the right cardiac contour. In the presence of mitral regurgitation of a higher degree one notices that these two arches show pulsations in opposite directions. The upper arch corresponds to the left auricle and shows a forceful lateral movement during systole, while the lower arch (right auricle) simultaneously reveals a smaller movement inward. Mahaim² was the first to describe this seesaw movement, and Roesler³ interpreted it correctly when he ascribed the movement of the upper arch to the impact of the regurgitating blood and the pulsations of the caudal arch as transmitted from the contracting right ventricle.

As the large left auricle bulges to the right, it may in certain cases transmit its pulsations against the ventral wall of the chest, giving rise to a systolic pulsatory propulsion which, even without the aid of a roentgenographic study, may permit one to diagnose the underlying condition. This protrusion of the thoracic wall is noted beyond the right sternal border. It may be differentiated from other pulsations along the parasternal portions of the ribs, as encountered in disease of the mitral valve, in that it causes a shock against the thoracic wall

Translated by Hugo Roesler, M D, Philadelphia

From the *Herzstation*, Dr. Hans Horst Meyer and Dr. Emil Zak, directors

1 Stoerk, O. Zur Topographie des Mediastinum bei normaler und bei pathologischer Herzform, *Ztschr. f. klin. Med.* **69** 32, 1910

2 Mahaim, I. Un symptôme radiologique de l'anévrisme de l'oreillette gauche, *Schweiz. med. Wchnschr.* **57** 183, 1927

3 Roesler, H. Rechtsseitige, mitgeteilte Hiluspulsation bei aneurysmatischer Erweiterung des linken Vorhofes, *Fortschr. a. d. Geb. d. Röntgenstrahlen* **40** 1017, 1929

in a large area, extending between the second and the sixth rib to the right midclavicular line. Such a widespread heaving of the right wall of the chest cannot be interpreted as a simple associated movement, as it may accompany the action of a hypertrophied right ventricle. Percussion reveals in association with it an extension of the cardiac dulness far to the right. The content of such an aneurysmatically enlarged right auricle may be up to 2 liters, and the rest of the heart, though not small, looks like an appendix to the left auricle. The left auricle embraces the right auricle from behind and may extend beyond it for more than a handbreadth when visualized from in front.

Roentgenograms show it as a big bulge silhouetted at the right border with its convexity directed to the right and upward (Lutembacher⁴). The left auricle may form the whole right cardiac border, and within one notices the lateral contour of the denser shadow of the right auricle. The posterior (lower) lobe of the right lung becomes atelectatic and is displaced on the right and upward, the left auricle is found in broad contact with the ventral wall of the chest and the diaphragm, forming a depression on the latter (Goedel⁵). The forceful regurgitation of blood in cases of mitral regurgitation may thus create a pulsation of larger portions of the right side of the chest. These pulsations may be demonstrable as far as the right axilla and occasionally cause a jerky movement of the whole chest, directed to the right during systole.

Bedford⁶ described such pulsations in association with an aneurysmatically dilated left auricle in two cases, and my colleagues and I have observed it in eight instances.⁷ In all these cases high grade mitral regurgitation was present. The following case serves as a typical example.

P. A. was a woman aged 26. In this case the clinical diagnosis was mitral stenosis and regurgitation with auricular fibrillation. The patient was digitalized and showed no definite signs of cardiac failure. Examination revealed immediately a widespread forceful pulsatory movement on the right side of the chest (fig. 1). The center of pulsation, where the systolic propulsion of ribs and soft tissue was most marked, was in the right midclavicular line between the fourth and the fifth intercostal space. Associated with it was a definite movement directed to

4 Lutembacher, R. Aneurisme de l'oreillette gauche, *Arch d mal du cœur* **10** 145, 1917, Deux nouveaux cas d'anévrisme de l'oreillette gauche, *ibid* **11** 434, 1918.

5 Goedel, A. Eine ungewöhnliche Form der Herzvergrösserung (enorme Vorhofvergrösserung) bei Mitralstenose, *Wien klin Wchnschr* **42** 427 (April 4) 1929.

6 Bedford, D. E. Two Cases of Aneurysmal Dilatation of the Left Auricle, *Proc Roy Soc Med* **20** 328, 1927.

7 Dressler, W. Die Brustwandpulsationen als Symptome von Herz- und Gefasskrankheiten, Vienna, Wilhelm Maudrich, 1933.

the right and upward. The pulsation affected almost the whole right side of the chest and extended cephalad as far as the second rib and caudad to the costal arch. Its intensity was diminished in the region below the sixth rib, i. e., in the hepatic area. A definite systolic shock was palpated in the right axilla (fig 1 *B*). The pulsation on the right actually governed the movement of the whole chest, which showed an abrupt jerky systolic shift to the right and cephalad. This movement was palpated over the right shoulder, and it could even be noticed through a blanket. The sternum and a small area along its left border, extending from the third rib to the costal arch, participated in this pulsatory propulsion of the right side of the chest. The rest of the whole left side of the chest revealed a definite systolic depression which affected soft tissues as well as ribs. This movement was more marked in the lateral and caudal aspects below the sixth rib and was combined with the movement to the right. With the exception of the aforementioned small medial area, the whole left side of the chest appeared to be forcefully "drawn in" during systole. This movement was apparently caused by the pull of the systolic bulge on the right. In addition, an aspiratory effect, caused by the bulging right wall of the chest as well as by the full emptying of the left ventricle (mitral regurgitation), undoubtedly played an important rôle. This explains why the area of depression extended to the back, where there was

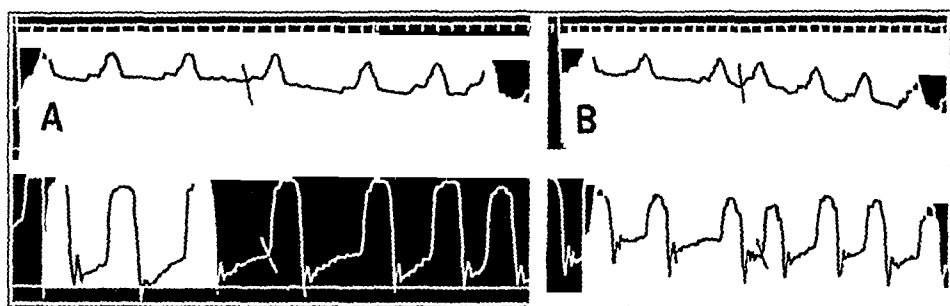


Fig 1 (patient P A) —The graph demonstrates the systolic propulsion of the right side of the chest caused by the pulsating left auricle. The lower graph is for the apical thrust. The upper graph is for the (*A*) third intercostal space, 4 cm outside the right midclavicular line, and (*B*) for the fourth intercostal space in the right anterior axillary line.

a definite systolic depression of the soft tissues and ribs over the left caudal aspect, lateral to the scapular line (Broadbent's sign). The development of these unusually forceful pulsations was obviously enhanced by the flexible skeleton of the young slender patient. The apical thrust was easily felt as a forceful elevation, but it was poorly visible within the diffuse depression on the left side, it was located in the sixth intercostal space, 2 fingerbreadths beyond the left midclavicular line, and was definitely widened and of increased resistance.

Percussion revealed that the cardiac dullness extended 4 fingerbreadths beyond the right sternal border in the fourth intercostal space. There was absolute flatness over the sternum, extending from Louis' angle to the ensiform process. To the left of the left sternal border was an area of dullness that was 2 fingerbreadths wide in the second intercostal space and 4 fingerbreadths wide in the third intercostal space.

Auscultation revealed over the apex a long, loud, blowing systolic and a short, booming diastolic murmur. The latter was accompanied with a palpable diastolic thrill. The systolic murmur was heard over the whole cardiac area, though with

less intensity The pulmonic second sound was moderately increased The action of the heart was irregular, auricular fibrillation being noted in the electrocardiogram The heart rate was 84 The blood pressure was 115 systolic and 55 diastolic The liver extended for 3 fingerbreadths below the costal arch in the right mid-clavicular line, it revealed a weak systolic pulsation The same findings were present over the veins of the neck Cyanosis and edema were not noted

Roentgenograms showed an enlarged silhouette of mitral configuration, with a transverse diameter of 20 cm (fig 2) The lateral wall of the chest was reached on the left side and was approached on the right side The left auricle was enormously enlarged, forming the whole right contour of the heart, and was the cause of the extensive dilatation to the right It rested directly on the diaphragm Within the cardiac shadow was a denser nuclear shadow, which corresponded to the right auricle The dome of the left auricle projected toward the right axilla at the level of the fourth intercostal space The right auricle was dilated likewise and was embedded within the left auricle

Several facts prove that the pulsations of the right wall of the chest were caused by the regurgitation of blood into the aneurysmatically enlarged left

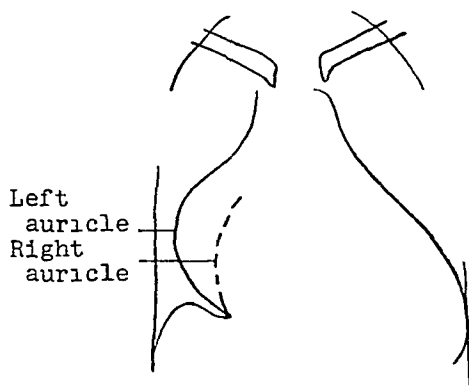


Fig 2—An orthodiagram, showing the large silhouette with the mitral configuration The new right cardiac border was formed by the aneurysmatically enlarged left auricle The original right cardiac border, as formed by the right auricle, is seen within (dash line)

auricle First, this phenomenon could be observed only in those cases in which high grade mitral regurgitation was present, second, because fluoroscopic observation revealed a forceful lateral systolic pulsation of the contour of the left auricle, corresponding to the direction of the regurgitating blood, third, because fluoroscopic observation revealed in every instance that the maximum pulsation of the thoracic wall coincided with the convexity of the contour of the left auricle

Such a pulsation of the aneurysmatically dilated left auricle is remarkably often associated with a ventricular venous pulse in the veins of the neck and in the liver It seems improbable that this finding should always be attributed to associated tricuspid regurgitation, particularly because of the unusually good compensation, which may last for years It is conceivable that the left auricle, which is in close con-

tact with the right auricle and embraces it from behind and pushes it ventrad, imparts to it its forceful systolic pulse which then will be transmitted to the veins. It must be recalled also that the left auricle, by displacing the lung, comes into direct contact with the diaphragm and thus may directly transmit its pulsations to the liver.

Pulsations of the thoracic wall which are caused by the left auricle may be recognized without difficulty even in the presence of tricuspid regurgitation. The auricular pulsations show their maximum strength above the lung-liver border, approximately at the level of the fourth intercostal space, while pulsations of the thoracic wall transmitted from the pulsating liver are, of course, best felt over the caudal third of the chest.

SUMMARY

A pulsating propulsion of the right wall of the chest is observed in cases of aneurysmal dilatation of the left auricle to the right. Mitral regurgitation is a prerequisite, and the pulsations are caused by the impact of the blood regurgitating into the left auricle. The maximum of these pulsations as a rule is found in the right midclavicular line between the fourth and the sixth rib, and pulsations may be observed as far as the right axilla.

OPTIC NEURITIS IN HYPERTHYROIDISM

REPORT OF A CASE WITH REVIEW OF THE LITERATURE

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AND

GABRIEL A SCHWARZ, M D

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Edematous and inflammatory diseases of the optic nerves are not always manifestations of a local lesion. In fact, it is known that these nerves, although well protected from direct injury, are often involved by disease processes that are far removed from the eyeball itself. Disease of the optic nerves may be the first indication of extracranial disease. From a review of the literature on the etiology of optic neuritis table 1 has been prepared (Fuchs¹). It may not be entirely complete, but it serves to illustrate the many diverse conditions that have been reported as affecting the optic nerves.

It is obvious from the multiplicity of the reported causes of optic neuritis that in a given case it is difficult to settle on any one etiologic factor to the satisfactory exclusion of all others. In spite of this, we feel justified in reporting a case of optic neuritis as illustrative of one of the rarer causes of this condition, namely, hyperthyroidism.

REPORT OF CASE

L L, a woman aged 30, was admitted to the service for patients with thyroid disease of the late Dr Charles H Frazier at the Hospital of the University of Pennsylvania on March 29, 1936, complaining of "swelling of the neck" and insomnia. The patient had apparently been in good health until February 8, less than two months before admission to the hospital, when she had an attack of "intestinal grip." The symptoms at this time consisted of general malaise, vomiting, fever, loss of appetite and weakness. The patient remained in bed for two weeks. The temperature slowly subsided, but the malaise and weakness continued. A physician was called, and the swelling in the neck was noted for the first time. Then insomnia, nervousness and tremors began to develop. The patient lost 22 pounds (10 Kg), the weight being reduced from 110 to 88 pounds (50 to 40 Kg), a loss of 20 per cent of the total body weight, within the period of illness preceding her admission to the hospital. She had had no visual distur-

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1 Fuchs, E. Disease of the Eye, ed 15, revised by M Salzman and translated by E V L Brown, Philadelphia, J B Lippincott Company, 1935, pp 395-398.

bances She had experienced some dyspnea on exertion since the onset of the "grip," and she believed that she had had some edema of the ankles evenings during the week preceding her entrance into the hospital She had been bothered by a dry, nonproductive cough The expected menstrual period in February had not occurred, and she had not menstruated since The past, family and social histories contained no pertinent facts

Physical Examination—The pulse rate was 140 per minute, the respiratory rate 28 per minute and the temperature 98 F The blood pressure was 140 systolic and 80 diastolic The patient was nervous and apprehensive There were generalized tremors of the body Examination of the fundi revealed optic neuritis The details of this and subsequent examinations of the eyegrounds and visual acuity are given in table 2 There were lateral nystagmoid movements on extreme lateral gaze in both directions Except for a suggestion of exophthalmos on both sides, there was no external ocular sign of thyrotoxicosis The nasal septum was slightly deviated The oral cavity presented dental sepsis and chronically infected

TABLE 1—*Etiologic Factors Reported in Disturbance of the Optic Nerve*

I Diseases of the central nervous system	
1	Lesions producing increased intracranial pressure brain tumor, brain abscess, hydrocephalus, etc
2	Infections syphilis, tuberculosis, encephalitis, meningitis and poliomyelitis
3	Multiple sclerosis, syringomyelia and Schilder's disease
II	Generalized infections acute exanthemas, diphtheria, pertussis, mumps, pneumonia, grip, influenza, Malta fever, Weil's disease, malaria, typhus fever, tularemia, frambesia, etc
III	Other general systemic diseases diabetes, nephritis, hypertension, etc
IV	Blood dyscrasias anemias, leukemias and purpura haemorrhagica
V	Focal infections infections of teeth, tonsils and adenoids, sinusitis, mastoiditis and parotitis
VI	Exogenous toxins lead, alcohol, iodoform, arsenic, carbon disulfide, thallium, apiol, nicotine, tryparsamide, acetarsone, naphthalene and a host of others
VII	Orbital conditions tumor, infection, trauma, etc
VIII	Endocrine disturbances hyperthyroidism, hypothyroidism, pituitary disease, etc
IX	Gynecologic phenomena pregnancy, lactation, eclampsia, puberty, menstrual disturbances and menopause
X	Miscellaneous vitamin deficiency, antirabic inoculations, protein therapy, heredity, helminths and "cryptogenic" forms

tonsils A mucopurulent postnasal drip was noted in the oropharynx The thyroid gland was moderately and diffusely enlarged Percussion of the area over the heart revealed slight cardiac enlargement, and a systolic murmur was heard over the pulmonic area The deep reflexes were generally hyperactive Abortive ankle and patellar clonus, with a suggestion of a bilateral Babinski sign but none of its confirmatory signs, comprised the neurologic findings

Laboratory Examination—The basal metabolic rate on the day following the patient's admission to the hospital was plus 82 per cent All subsequent values for the metabolic studies and their relationship to the weight, pulse rate and course of the disease are presented in table 3

An intravenous phenolsulfonphthalein test showed 30 per cent excretion of the dye in fifteen minutes, 30 per cent in the next forty-five minutes and fifteen per cent at the end of two hours, giving a total excretion of dye of 75 per cent The urea nitrogen content of the blood was 9 mg per hundred cubic centimeters The urea clearance was 52 per cent of the average normal function Details of the more complete urinary studies are recorded in table 4

Roentgenographic study of the head revealed enlargement of the pituitary fossa and equivocal evidence of increased intracranial pressure

Gastric analysis with histamine showed achlorhydria

The pressure of the cerebrospinal fluid varied from 80 to 100 mm of water. The protein content of the fluid was 125 units (normal). One lymphocyte and 2 erythrocytes were noted per cubic millimeter of cerebrospinal fluid. The Was-

TABLE 2—*Eyegrounds and Visual Acuity*

Date, 1936	Vessels	Retina			Acuity*	
		Hemorrhages	Exudates	Disks	Right	Left
4/ 1	Arteries contracted and tortuous, veins engorged	Fresh, few flame shaped, bilateral	None	Margins fluffy, normal color, good vascularity, swelling, 1 diopter on left, 2 diopters on right		
4/ 2					6/30	6/60
4/ 9					6/12 —2 s c	6/15 s c
4/13	Arteries normal, veins slightly engorged	None on left, few right	None	Unchanged, bilateral swelling of 2 diopters		
4/17					6/12 —2 c c	6/12 —1 c c
4/23	Normal	None	None	Swelling of 1 diopter on left, 1 diopter on right	6/ 9 —1	6/12 —3
6/ 2	Normal	None	None	Margins of disks still fuzzy, bilateral swelling of 1 diopter	6/12 —1 c c	6/12 —2 c c
6/12					6/12 —2 c c	6/ 9 —3 c c
6/19					6/12 —3 c c	6/12 —3 c c
10/27					6/15 —1 c c	6/12 —1 c c
10/28	Vessels moderately full and tortuous	None	None	Margins faintly hazy, no swelling, color normal		

* s c indicates without correction, and c c, with correction

TABLE 3—*Basal Metabolic Rate, Pulse Rate and Weight Throughout the Treatment*

Date, 1936	Basal Metabolic Rate, Plus %	Weight, Pounds	Pulse Rate per Minute
3/30	82	87	120
4/ 4	44	81	100
4/ 7	36	80	96
4/11	33	79	102
4/14	31	83	116
Operation, right lobectomy			
4/24	28	81	92
6/ 2	56	102	126
6/ 5	49	101	124
6/ 9	41	103	122
Operation, left lobectomy			
6/19	31	102	92
9/23	1	112	100

Sermann test of the fluid gave a negative reaction, and the colloidal gold readings were 0000000000

The protein content of the blood serum was 47 per cent, and the chloride content was 103.4 milliequivalents per liter. The blood count on the day following the patient's admission to the hospital showed erythrocytes, 4,300,000, leukocytes, 7,600, and hemoglobin (Sahli), 72 per cent. The Wassermann reaction of the blood was negative.

Course—On April 2 the patient was started on sedation, iodine therapy, enforced rest in bed and a high caloric diet. She reacted well to the treatment and showed such definite clinical improvement that subtotal thyroid lobectomy on the right was performed by Dr. Julian Johnson on April 18. The postoperative course was not unusual. The wound healed by primary intention, and the patient was discharged on April 24, with a basal metabolic rate of plus 28 per cent. She was to receive iodine therapy regularly and was instructed to return in six weeks for the second stage of the operation.

After discharge the patient steadily improved until the last week in May. She then began to notice increasing nervousness and palpitation. She was readmitted to the hospital on June 6. The pulse rate was 120 per minute. The blood pressure was 140 systolic and 80 diastolic. The patient weighed $104\frac{1}{4}$ pounds (47.5 Kg.). The left lobe of the thyroid gland was found to be diffusely enlarged. The heart was normal in size. A blood count revealed 4,400,000 erythrocytes, 7,800 leukocytes and a hemoglobin value of 88 per cent. The basal metabolic rate was plus

TABLE 4—Renal Studies, Twenty-Four Hour Concentration Test

	Normal Figures	Examinations		
		4/17	6/7	10/27
Specific gravity	1.025 or more	1.021	1.028	1.032
Amount of urine, cc	380 average	407	546	146
Oasts, thousands	5 or less	291	79	67.5
Red blood cells, thousands	500 or less	1,000	1,200	600
Epithelial cells and leukocytes, millions	2 or less	7.3	2.1	0.5
Blood urea nitrogen after restriction of fluids, mg. per 100 cc	Up to 21	21.1	21.7	16.7
Urea clearance, %	55 to 100	52	72	60
Protein in urine, Gm. in 12 hours	0.1 or less	0.55	0.3	0.6
Plasma protein, Gm. per 100 cc	6 to 7	6.56		6.48

56 per cent. A roentgenogram of the sinuses showed the right antrum to be clouded, but an otolaryngologist said he considered that the sinuses presented no clinical evidence of active disease. The patient was again treated with rest, sedation, iodine and a high caloric diet. The basal metabolic rate finally dropped to plus 41 per cent. On June 13 lobectomy on the left was performed by Dr. Robert Brown. The immediate postoperative course was stormy, but the patient recovered and was discharged with a basal metabolic rate of 31 per cent on June 20.

Subsequently the patient was followed in the section for patients with endocrine disorders of the outpatient department of the University Hospital. When last seen, in October 1936, she did not present any clinical signs and had no symptoms of thyrotoxicosis. Although the pulse rate was still a bit hurried, the basal metabolic rate was plus 1 per cent. The details of the results of studies of the kidneys, fundi, visual acuity and visual fields are given in the accompanying tables and charts.

REVIEW OF THE LITERATURE

According to the number of cases of disturbance of the optic nerves associated with hyperthyroidism that have been recorded in the litera-

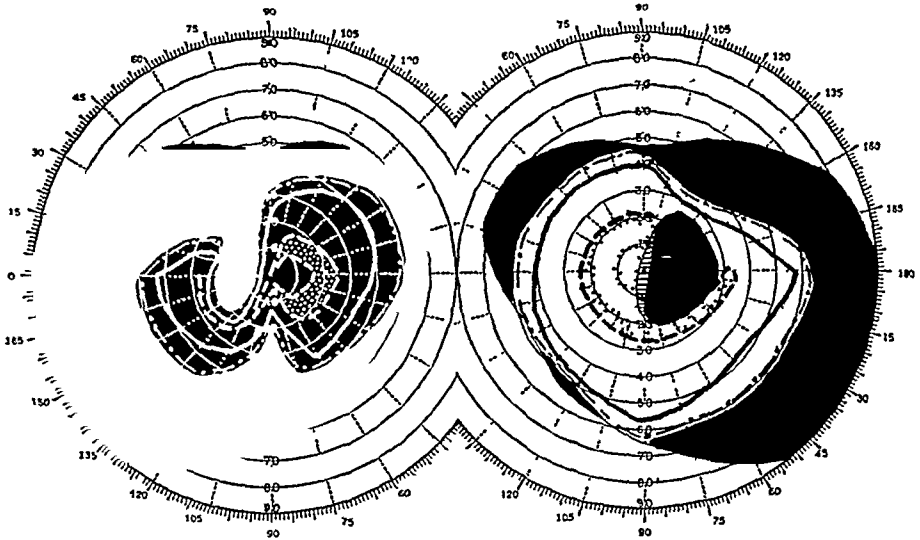


Chart 1—These visual fields were taken before treatment with iodine was begun. Note the tendency toward bitemporal heteronymous hemianopia and the enlargement of the blindspots. In charts 1 to 8 the solid line indicates the field of vision as shown by a 1 degree white test object, the dash and dot line, that shown by a 2 degree white test object, the dash line, that shown by a 1 degree red test object, and the dotted line, that shown by a $\frac{1}{2}$ degree red test object. The blackened area indicates absolute scotoma, the horizontally shaded area, scotoma for a 1 degree white test object, the vertically shaded area, that for a 1 degree red test object, and the dotted area, doubtful scotoma for a 1 degree red test object.

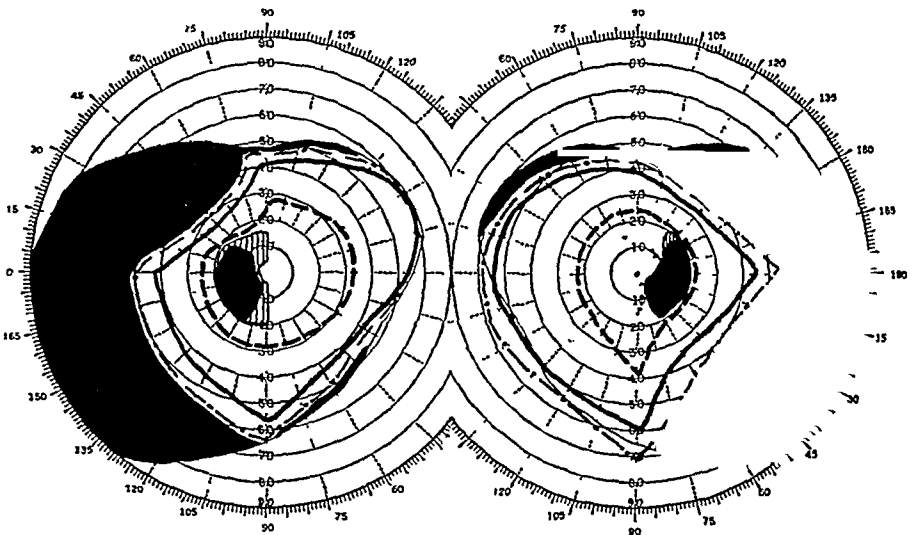


Chart 2—These fields were obtained after one week of treatment. Note the marked improvement.

ture, the condition must be rare. In 1921 H. Sattler² and Behr³ published excellent reviews of this subject. Sattler reported the case of a 52 year old man who suffered from exophthalmic goiter for eight years before thyroidectomy was performed. He had blurring of vision and slight pallor of the temporal half of each optic nerve head, with considerable reduction in the visual acuity. There was marked improvement of the disturbance of the optic nerves (retrobulbar neuritis), with recession of the symptoms of hyperthyroidism after thyroidectomy. Sattler collected from the literature reports of thirteen other cases of disease of the optic nerve due to thyrotoxicosis. Behr reported four causes of Dercum's disease with changes in the optic nerves. He then discussed the production of optic neuritis by certain endogenous toxins, particularly in hyperactivity of the thyroid gland. He added reports of four further cases cited in the literature.

In addition to these cases we have found that von Hippel⁴ recorded four cases of changes in the optic nerves associated with hyperplasia of the thyroid gland. However, he reported no basal metabolic determinations in any of these cases, and a study of his protocols leads one to believe that these were not cases of true hyperthyroidism. Keogh⁵ reported a case of exophthalmic goiter in which the immediate post-operative period there developed partial blindness associated with atrophy of both optic nerves. He suggested that this was due to some undetermined form of intestinal toxemia associated with hyperthyroidism.

Since the publication of the aforementioned reviews few cases of optic neuritis caused by hyperthyroid disease have been reported in the literature. In his textbook on the eye Moore⁶ stated that he had noted one case of retrobulbar neuritis associated with exophthalmic goiter. More recently, this author,⁷ in discussing ocular diseases in exophthalmic

2 Sattler, H. Ueber einen Fall von Neuritis nervi optici retrobulbaris als Frühsymptom der Basedowschen Krankheit, *Wien med Wchnschr* **71**:1084-1088 1921

3 Behr, C. Sehnervenentzündungen bei Störungen der inneren Sekretion im Verlauf der Adipositas dolorosa (Dercumschen Krankheit), *Deutsche Ztschr f Nervenhe* **71** 275-296, 1921

4 von Hippel, E. Toxische Sehnervenerkrankung mit seltener Aetiologie, in von Graefe, A., and Saemisch, E. T. *Handbuch der gesamten Augenheilkunde*, Berlin, Julius Springer, 1923, vol 7 B, pt 2, pp 401-405, Das Abderhaldensche Dialysierverfahren beim Glaukom sowie bei einigen Sehnervenerkrankungen, *Arch f Ophth* **90** 198-245, 1915

5 Keogh, C. H. Graves' Disease. A Case with Post-Operative Amblyopia, *New York M J* **104** 457, 1916

6 Moore, R. Foster. *Medical Ophthalmology*, Philadelphia, P. Blakiston's Son & Co, 1925, pp 219-220

7 Moore, R. Foster, in Berens, C. *The Eye and Its Diseases*, Philadelphia, W. B. Saunders Company, 1936, p 817

goiter, stated that these symptoms are "limited to the adnexa of the eyeball" and that "no pupillary or fundus changes occur" Wiener⁸ mentioned under unusual ocular complications of goiter atrophy of the optic nerve and neuroretinitis Naffziger and Jones⁹ in a report of six

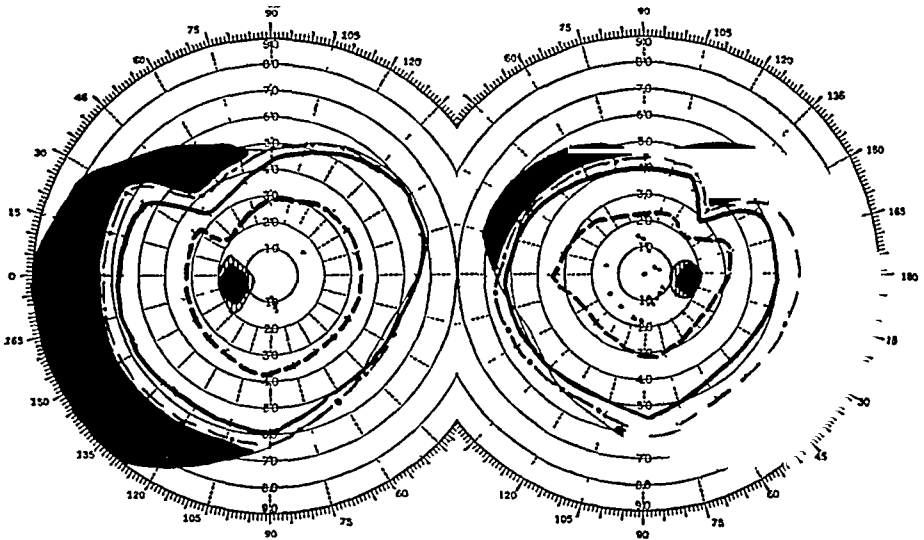


Chart 3—These fields were taken the day before the first stage of thyroid lobectomy. There has been remarkable improvement still with a tendency to defects in the upper quadrants.

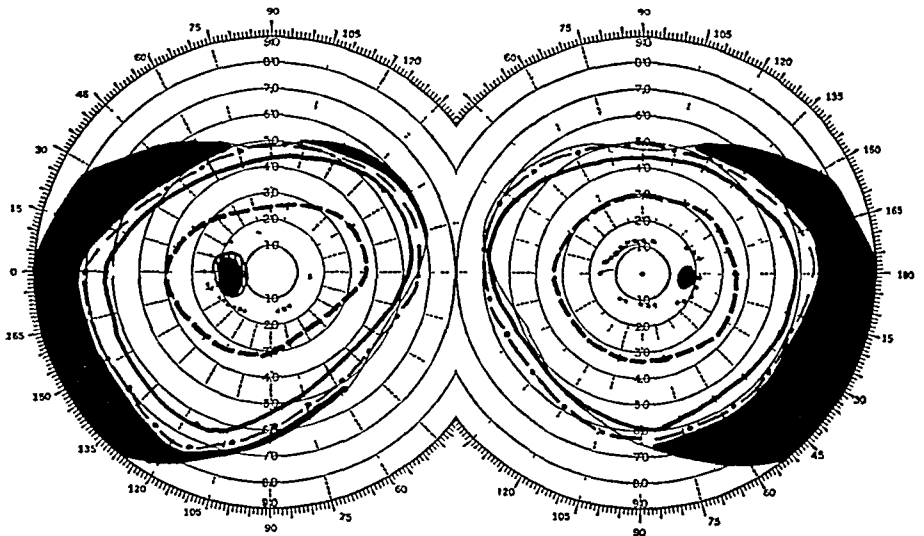


Chart 4—Five days after the first stage of the operation. The blindspots are now nearly normal in size, and the quadrantic defect is no longer present.

⁸ Wiener, M. Diseases of the Eye, J. Missouri M. A. **23** 211-212, 1926.

⁹ Naffziger, H. C., and Jones, O. W., Jr. Surgical Treatment of Progressive Exophthalmos Following Thyroidectomy, J. A. M. A. **99** 638-642 (Aug. 20) 1932.

cases of progressive exophthalmos following thyroidectomy noted swelling and atrophy of the optic disks in five cases. In addition Friedenwald¹⁰ reported a case of choked disk associated with a similar type of exophthalmos. However, Bothman¹¹ had pointed out that distur-

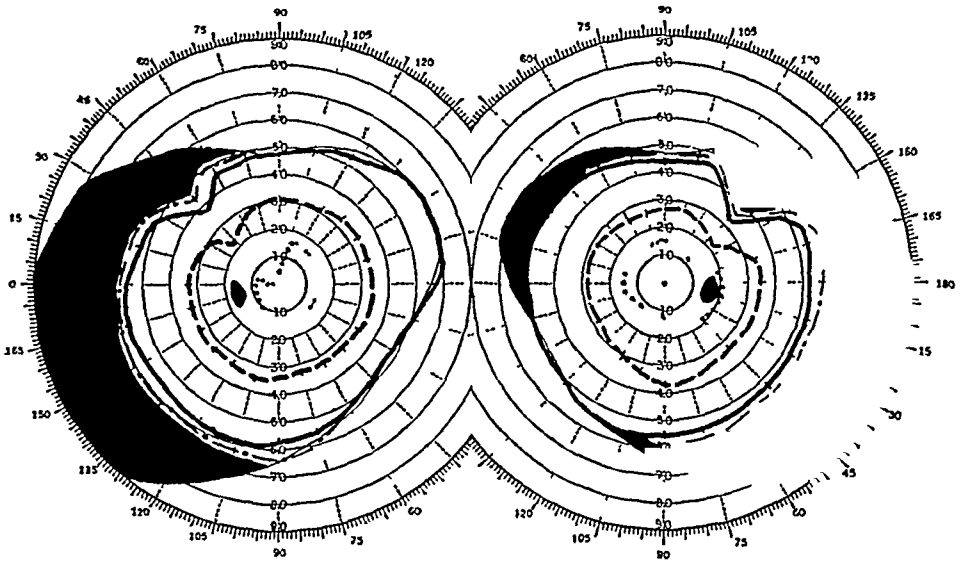


Chart 5—After six weeks the visual fields have regressed, along with the return of thyrotoxic symptoms. Again hemianopia is suggested, and the defect in the upper outer quadrant is present.

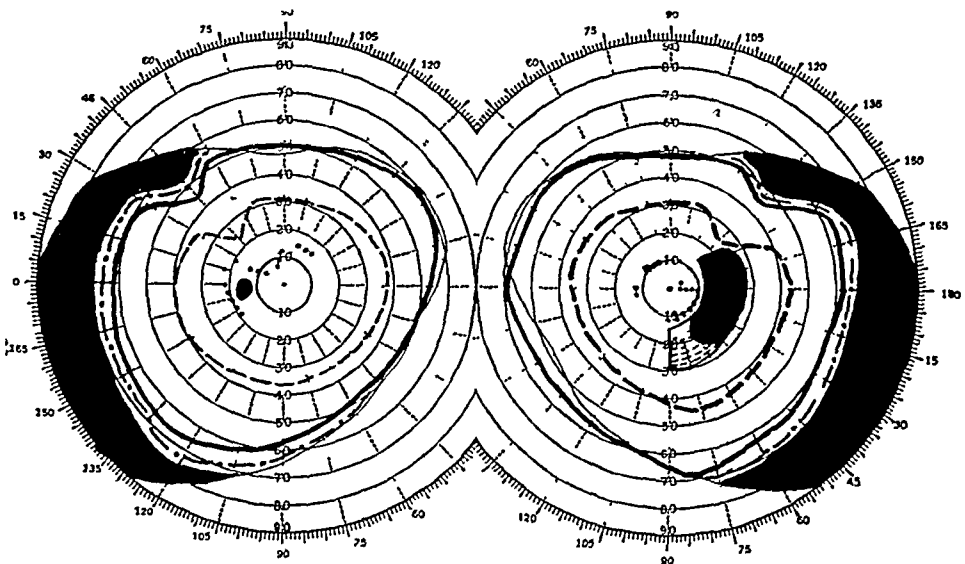


Chart 6—Ten days after further treatment in the hospital improvement is again noted. The blindspot in the left eye is definitely enlarged.

¹⁰ Friedenwald, J. S. Orbital Myositis and Choked Disk in Exophthalmic Goitre, *Ann Surg* **96** 995-997, 1932.

¹¹ Bothman, L. Endocrines in Ophthalmology, *Illinois M J* **65** 226-235, 1934.

bances of the optic nerves are not infrequently seen when the eyeball protrudes 25 mm or more, and it is likely that the changes in the optic nerves associated with this type of exophthalmos are mechanical in origin, as suggested by Naffziger¹² In a study of the ocular signs in

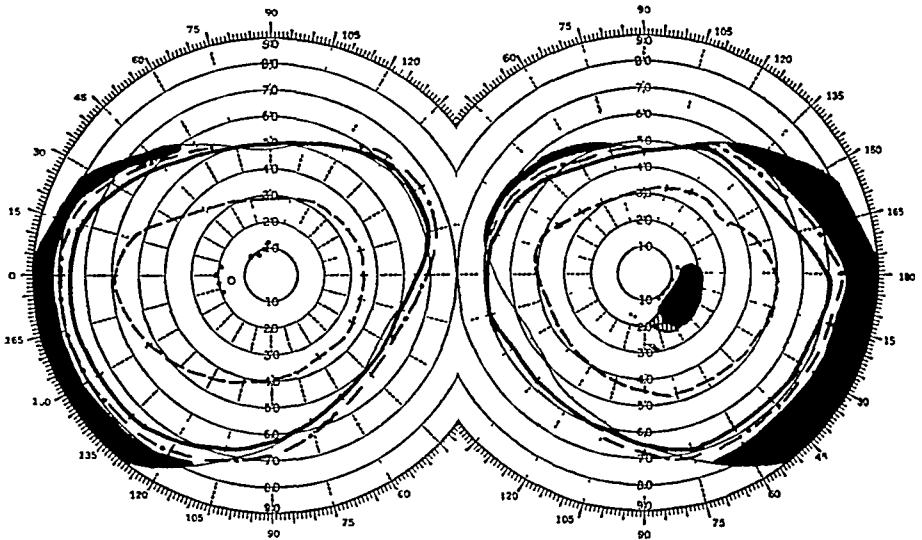


Chart 7—These visual fields were obtained about six days after the second thyroid lobectomy had been performed

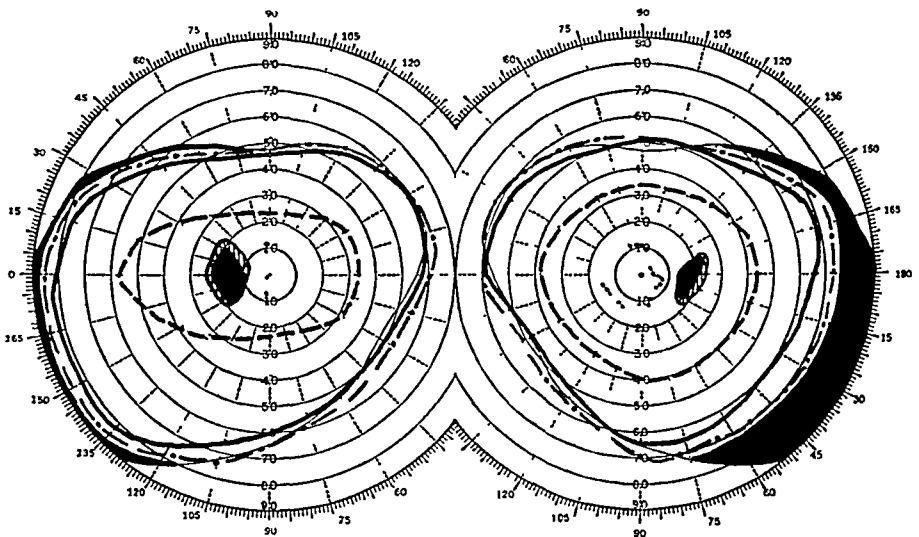


Chart 8—These fields were obtained four months after the final operation. There are no signs or symptoms of hyperthyroidism. The basal metabolic rate was plus 1 per cent.

¹² Naffziger, H. C. Pathologic Changes in the Orbit in Progressive Exophthalmos, with Special Reference to Alterations in the Extra-Ocular Muscles and the Optic Disks, *Arch Ophth* 9 1-12 (Jan) 1933

one hundred unselected cases of hyperthyroidism Holloway, Fry and Wentworth¹³ noted "no atrophy, optic neuritis or choking of the discs"

Observations on thyroid feeding, both in human beings and in experimental animals, lend further support to the concept of the etiologic relationship between hyperthyroidism and changes in the optic nerves Coppez¹⁴ reported on five patients with obesity who had been taking large doses of thyroid over long periods Visual disturbances developed resembling those of tobacco amblyopia with central scotomas The visual acuity was reduced to less than 10 per cent of normal After stopping the medication all of these patients recovered Aalbertsberg¹⁵ treated a myxedematous patient with dried thyroid gland, and the patient subsequently lost the vision in both eyes Ophthalmologic examination revealed hyperemia of the disks After cessation of the thyroid medication the vision in the right eye improved, while atrophy of the left optic nerve developed Standish¹⁶ has reported optic neuritis in patients who were taking thyroid for obesity Birch-Hirschfeld and Inouye¹⁷ fed increasing doses of thyroid substance to a number of dogs In one of the animals pallor of the optic disks developed, with contraction of the retinal arteries Histologic examination showed degeneration of the fibers of the optic nerves and destruction of the ganglion cells of the retinas

COMMENT

Several interesting questions arise from a study of our case First, was the thyrotoxic state the only active agent in the production of the optic neuritis? In order to prove this it would be necessary to establish the absence of an etiologic relationship of (1) the foci of infection in the teeth and tonsils and possibly that in the sinuses, (2) the renal disturbance and (3) the initial attack of "intestinal grip" All of these conditions have been reported as causes of inflammation of the optic nerve

We have already stated that the complete and satisfactory exclusion of all but one etiologic factor in a given case of this type is difficult However, there are certain considerations in this particular case which point to thyrotoxicosis as the chief, if not the sole, causative agent

13 Holloway, T B, Fry, W E, and Wentworth, H A Ocular Signs in One Hundred Unselected Cases of Goitre, J A M A **92** 35-41 (June 5) 1929

14 Coppez, H Nevrite optique par absorption de thyroïdine, Arch d'ophth **20** 656-662, 1900

15 Aalbertsberg, G Neuritis optica door het gebruik van schildklier, Nederl tijdschr v geneesk **2** 1125, 1902

16 Standish, cited by Bothman¹¹

17 Birch-Hirschfeld, A, and Inouye, N Experimentelle Untersuchungen über die Pathogenese der Thyreodiambyopie, Arch f Ophth **61** 499-523, 1905

An obvious but nevertheless convincing argument presents itself to minimize the possibility of any relationship between the foci of infection and the optic neuritis. The dental, tonsillar and sinus conditions have remained untreated and unchanged, the disease of the optic nerves has greatly improved.

The occurrence of disease of the optic nerves in renal dysfunction is, of course, well known. It is usually associated with uremia and hypertension. In the present case there was no history suggestive of nephritis. The slight elevation of the blood pressure with a wide pulse pressure was of the type frequently seen in thyrotoxicosis rather than that of renal disease. The special studies which revealed mild renal impairment were requested for the sake of completeness in studying this case. The clinical picture itself had not suggested them. It seems unlikely that changes in the eyegrounds of this nature and degree could be caused by the mild renal impairment present in this case. There was a slight change in the direction of improvement in the renal condition during the period of study.

Renal changes which in themselves were secondary to or at least associated with thyroid disease have been reported. Graupner¹⁸ found in two patients with severe hyperthyroidism who died in delirium shortly after operation degenerative changes in the renal epithelium, progressing even to necrosis in one case. Von Monakow¹⁹ described a case of hyperthyroidism with marked albuminuria and edema combined with poor elimination of chloride. Von Muller²⁰ reported the case of a 62 year old woman with definite goiter associated with secondary parenchymatous renal degeneration, as evidenced by a low concentrating power and high blood pressure (210 mm of mercury) with cardiac hypertrophy, persistent albuminuria, edema and pseudochyloous ascites. However, establishment of an etiologic relationship between the hyperthyroidism and the renal impairment in this case is not an object of discussion. The possibility of such a relationship has merely been suggested.

As far as the etiologic significance of "intestinal grip" is concerned, we wish to point out the all too frequent inclusive nature of such a diagnosis. From the description of the patient's symptoms and from the continuity of the symptomatology with that of the thyroid over-

18 Graupner. Nierenkrankung bei Basedowscher Krankheit, *Munchen med Wchnschr* **57** 1695, 1910.

19 von Monakow, P. Beitrage zur Kenntnis der Nephropathien, *Deutsches Arch f klin Med* **115** 224, 1914.

20 von Muller, F. Veroffentl a d Geb d Mill-Saw-Wes **65** 33, 1917, cited by von Volhard, F. Nieren und ableitende Harnwege, in von Bergmann, G, and Staehelin, R. *Handbuch der inneren Medizin*, Berlin, Julius Springer, 1931, vol 6, p 1052.

activity, one wonders if this was not really the acute onset of the thyrotoxic state and not a grippal infection

A study of the changes in the visual fields in relation to the fluctuation in the hyperthyroid state supplies the most convincing evidence in establishing thyrotoxicosis as the chief etiologic agent. First, the effect of preoperative iodine therapy is to be noted by comparing charts 2 and 3 with chart 1. The continued improvement after excision of the right lobe is shown in chart 4. During the period between the first and second stages of the operation the hyperthyroidism again increased, as indicated by the clinical picture and the basal metabolic rate. Concomitant with this was regression of the visual fields, as shown in chart 5. After the final lobectomy the visual fields improved more definitely and more completely than ever before (charts 7 and 8).

Another interesting question that arises in this case is that of the actual mechanism of the production of the changes in the optic nerves. Many authors believe this is due to a toxin produced by the thyroid gland, an endogenous toxin. In some cases, but certainly not in this one, the exophthalmos with retro-orbital pressure on the optic nerves is undoubtedly the etiologic factor. It may be that hyperthyroidism, a disease well known for its effect on the nervous system, sensitizes the optic nerve to the damaging influence of mild infections, renal disturbances and other disorders which alone would be harmless.

The type of disturbance of the visual fields, the suggested bitemporal heteronymous hemianopia and later the defects in the upper outer quadrants suggest chiasmal pressure from a swollen pituitary body. The edema of the optic nerve heads less readily yields to such an explanation. That there may be hypertrophy and hyperactivity of the pituitary gland with thyroid disease is possible. The increase in size of the pituitary fossa lends weight to this theory.

CONCLUSIONS AND SUMMARY

A case of thyrotoxicosis is presented in which optic neuritis was found to be an associated condition.

Despite the presence of other possible etiologic factors, because of the parallel fluctuations of the inflammation of the optic nerves and the thyrotoxic state, it is believed that hyperthyroidism was the chief cause of the optic neuritis.

It is pointed out that this condition must be rare and that the mechanism of the relationship is not definitely known.

The studies of the visual fields were made by Dr. Hazel Wentworth, the studies of the eyegrounds, by Drs. William Pettit and Wilfred Fry, and the special renal studies, by Dr. Eugene Landis.

GASTRIC ACID DURING RECURRENCES AND REMISSIONS OF DUODENAL ULCER

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CHICAGO

The control of gastric acidity is still considered the major objective of therapy by many gastro-enterologists who believe hypersecretion to be the most important etiologic factor in the genesis of ulcer. This concept is maintained despite the accepted fact that there exists a marked variation in acidity not only in the ulcer-bearing patient but also in the normal healthy person. We do not concur with the belief that there is any exact relationship between the degree of gastric acidity and the symptomatology or behavior of an ulcer.

Although the preponderance of clinical and experimental evidence definitely opposes the correlation of gastric acidity with the production either of gastric pain or of the ulcer itself, the majority of clinicians employ and teach the precepts of neutralization therapy. Some investigators are still ascribing etiologic and therapeutic significance to deviations from the so-called normal levels of gastric acidity in patients with ulcer. In an excellent review of the subject of the mechanisms of pain in gastroduodenal ulceration, Palmer and Heinz,¹ in 1934, concluded that the usual stimulus is the free hydrochloric acid of the gastric content. Terauchi and Watanabe² in the same year reported a series of observations from which they concluded that the acidity of the gastric juice is greater in duodenal than in gastric ulcer. In 1935 Delfino³ attempted to attribute diagnostic significance to the curves for acidity

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1 Palmer, W L, and Heinz, T E. The Mechanism of Pain in Gastric and Duodenal Ulcers. VII Further Observations, *Arch Int Med* **53** 269 (Feb) 1934

2 Terauchi, Y, and Watanabe, K. The Stomach Juice in Patients Suffering from Gastric and Duodenal Ulcers, *Jap J Gastroenterol* **6** 46, 1934

3 Delfino, V. A Contribution to the Study of Gastric Acid Secretion by Means of Fractional Analyses in Cases of Gastric and Duodenal Ulcers, *Pathologica* **27** 261 (April 15) 1935

of ulcer-bearing patients, as compared with those of normal persons as determined by fractional test meals

Huist's⁴ observations were the first to indicate the importance of increased intragastric tension in the production of distress in patients with ulcer and definitely minimized the acid factor. Ivy,⁵ Smith and Paul,⁶ Carlson,⁷ Hardt⁸ and others have concurred in observations that altered motor function resulting from spasm, particularly of the pylorus or of sensitized areas in the region of the ulcer, hyperperistalsis or a combination of these factors are concerned in the production of pain. Palmer⁹ reported that he was able to reproduce characteristic pain in patients with peptic ulcer under suitable conditions of susceptibility by the administration of 0.5 per cent solution of hydrochloric acid and in some cases with lower concentrations. In a further study he¹⁰ suggested the use of this procedure as a diagnostic test. Hardy¹¹ was unable to confirm Palmer's observations in a large series of patients.

Passing rubber balloons into the pyloric region of the stomach, Smith and Paul⁶ found that in each instance pain corresponded with the passage of a peristaltic wave, except in the instances of more severe pain, when there was apparent spasm of the pylorus. Such evidence is difficult to correlate with the theories of the school of Talma, Bonniager, Heusche, von Selms, Sippy, Jordan and Palmer, which emphasizes gastric acidity as the fundamental mechanism of pain in patients with ulcer.

In analyzing the abundant but controversial data in the literature on levels of gastric acidity in patients with peptic ulcer, we find that there have been no reports of repeated examinations of the gastric contents of individual patients over periods of from two to five years. The

4 Hurst, A. F., and Stewart, M. J. *Gastric and Duodenal Ulcer*, New York, Oxford University Press, 1929, p. 26.

5 Ivy, A. C. *Physiology of the Stomach. Studies on Gastric Ulcer*, Arch Int Med **25**: 6 (Jan) 1920.

6 Smith, F. M., and Paul, W. D. *Studies on the Mechanism of the Pain in Peptic Ulcer*, Ann Int Med **5**: 14, 1931.

7 Carlson, A. J. *Origin of Epigastric Pains in Cases of Gastric and Duodenal Ulcer*, Am J Physiol **45**: 81, 1917.

8 Hardt, L. L. J. *Studies of the Cause of Pain in Gastric and Duodenal Ulcers. II Peristalsis as the Direct Cause of Pain in Gastric Ulcers with Achylia and in Duodenal Ulcers*, Arch Int Med **29**: 684 (May) 1922.

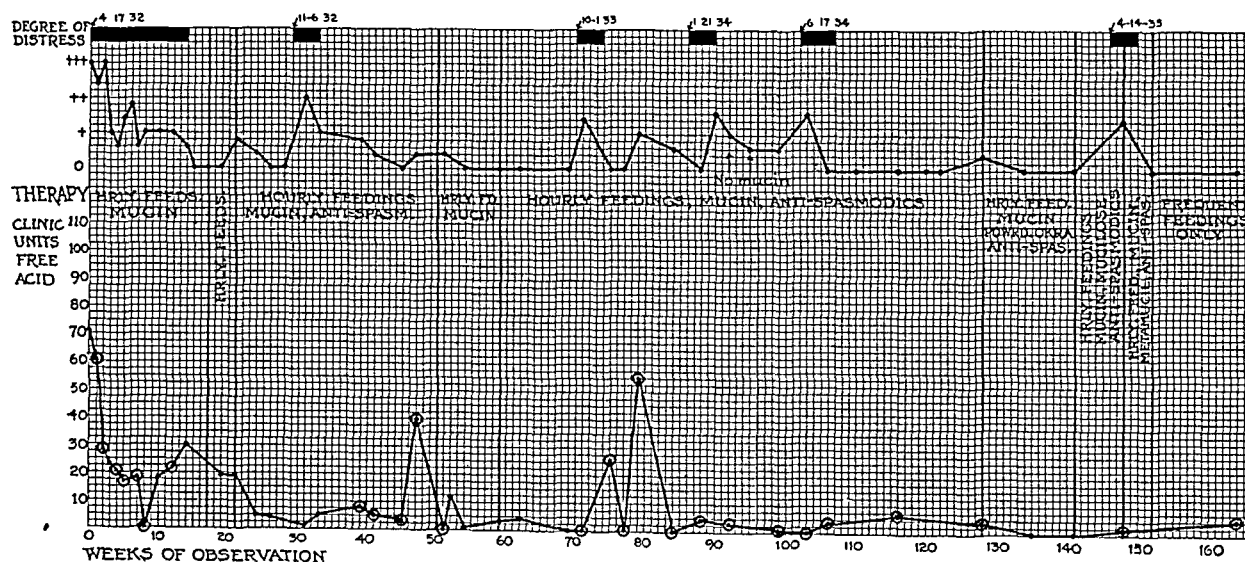
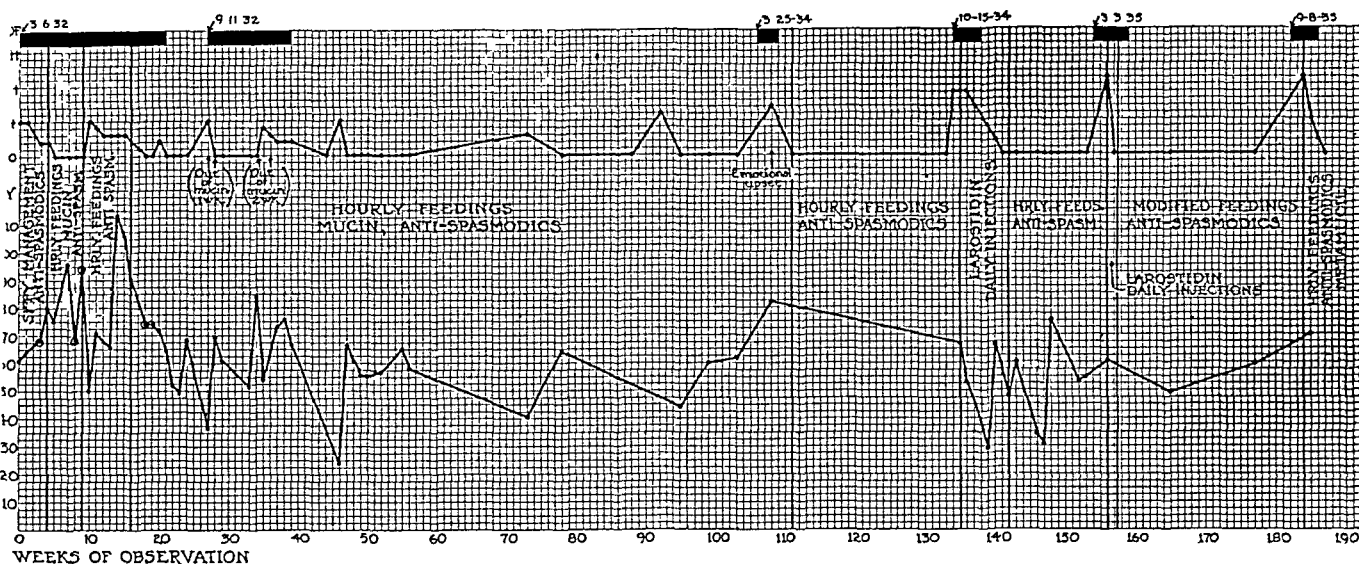
9 Palmer, W. L. *The Mechanisms of Pain in Gastric and Duodenal Ulcers: II The Production of Pain by Means of Chemical Irritants*, Arch Int Med **38**: 694 (Dec) 1926.

10 Palmer, W. L. *The "Acid Test" in Gastric and Duodenal Ulcer. Clinical Value of Experimental Production of Typical Distress*, J A M A **88**: 1778 (June 4) 1927.

11 Hardy, T. L. *The Rôle of Hydrochloric Acid in the Causation of Gastric Pain*, Lancet **1**: 711 (April 6) 1929.

Correlation of Individual Cases

Symptoms First Appeared Case No (Year)	Degree of Intrinsic Acidity	Weeks of Observation	Number of Gastric Analyses	Average Free Acid Level	Highest Free Acid Level	Lowest Free Acid Level	Recurrence During Study	Season of Recurrence			Acid Trend Just Prior to Recurrence			Acid Trend During Recurrence			Acid Trend During Distress						
								Winter	Spring	Summer	Fall	Higher	Lower	Significant	Not Significant	Higher	Lower	Significant	Not Significant	Higher	Lower	Significant	Not Significant
1 1923	++++	185	61	63.6	113	24	6	0	3	0	3	3	2	1	3	1	2	1	6	2			
2 1921	++++	164	43	13.0	71	0	6	1	2	1	2	0	2	4	2	1	3	2	2	4			
3 1926	++++	180	65	32.3	75	0	8	3	1	2	2	4	4	0	2	4	2	3	14	0			
4 1930	++++	125	48	24.5	53	0	5	1	1	1	2	4	1	0	1	4	0	3	3	1			
5 1924	++++	127	48	47.0	106	11	5	1	1	1	2	5	0	0	1	4	0	2	3	1			
6 1915	++++	92	52	43.1	71	12	3	0	1	0	2	2	0	1	1	2	0	1	0	6			
7 1931	++++	150	71	36.2	83	12	7	0	2	2	3	5	2	0	0	5	2	0	5	1			
8 1923	++++	147	41	46.0	84	30	6	0	2	1	3	2	3	1	1	3	2	2	3	2			
9 1923	++++	120	64	49.2	157	0	4	1	0	1	2	1	2	1	3	0	1	3	2	0			
10 1930	++++	241	70	30.0	70	2	6	1	3	1	1	1	3	2	3	1	2	2	4	1			
11 1917	++++	73	49	37.1	63	2	4	2	0	0	2	1	2	1	0	2	2	2	0	2			
12 1923	++++	117	49	42.6	74	2	3	0	1	0	2	1	1	1	2	0	1	3	0	0			
13 1928	++++	152	32	34.1	75	2	2	0	1	0	1	2	0	0	0	2	0	1	1	1			
14 1927	++++	161	30	51.3	99	24	4	1	2	0	1	2	1	1	2	2	0	1	3	1			
15 1925	++++	196	66	38.4	83	13	4	1	1	1	1	1	2	1	0	3	1	2	3	1			
Average 11.3 yr		148.6	53.2	39.2	85.8	8.9	4.8	12	21	11	29	34	25	14	21	34	18	23	51	23			
Totals																							
Control Series																							
16		152	37	29.7	59	4														2,995.0			
17		182	32	25.5	53	9														150.8			
18		180	56	27.7	51	0														73.0			
19		109	70	43.0	93	0														1,036.0			
20		142	52	32.5	55	7														51.8			
Average		153.0	49.4	31.0	63.2	4.0																	
															Total duration of observation, wk								
															Average duration of observation, wk								
															Total number of recurrences during study								
															Total number of gastric analyses								
															Average number of gastric analyses per patient								



patient is seldom observed until after the ulcer has arrived. The objective of our study was to determine the trend of free acid in patients with gastroduodenal ulcerative disease during periods of recurrence and remission, to investigate the relationship between the levels of acidity and the appearance of distress and to evaluate the response of gastric acidity to therapy over long intervals.

METHODS AND MATERIAL

The patients selected for this study were regularly seen in the clinic for patients with gastro-intestinal disorders in the outpatient department of St. Luke's Hospital. The criteria for selection were the duration of observation, the degree of intractability of the ulcer and the number of gastric analyses performed for each patient. All the patients were ambulatory during the study and were followed at regular

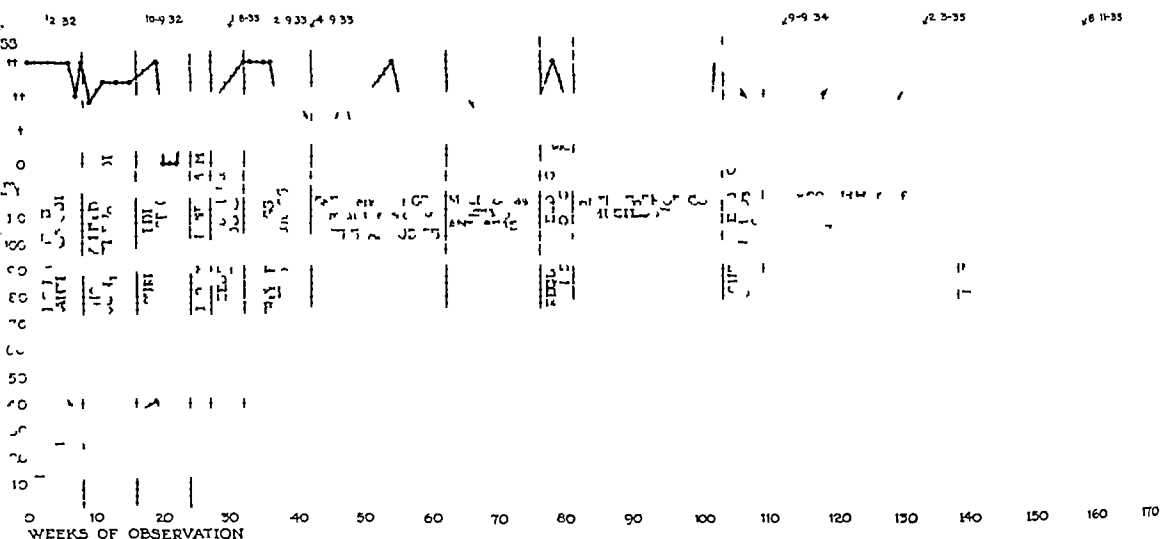


Chart 3—E B, a white man aged 26, had an appendectomy in 1926 for relief of ulcer-like distress, with no success. A diagnosis of duodenal ulcer was first made in 1927. Since then he had been attended by nine physicians, three of whom advised surgical intervention. This patient was studied for three years and eight months. Calcium carbonate and sodium bicarbonate were administered as indicated.

In the seventy-fifth week tri-calsate, a proprietary preparation containing tri-basic calcium phosphate $\text{Ca}_3(\text{PO}_4)_2$ and sodium citrate, was administered.

intervals by means of gastric analyses, stool examinations and roentgenologic studies. A few patients were hospitalized for short periods. These intervals have been indicated in the individual graphic analyses.

Of the twenty patients reported on in this series, fifteen had duodenal ulcer and five were controls, in whom no ulcer could be demonstrated but who received ulcer therapy similar to that given the patients with duodenal ulcer. The average time of observation for each patient was one hundred and fifty and eight-tenths weeks. A total of one thousand and thirty-six gastric analyses were performed, with an average of fifty-one and eight-tenths Ewald test meals per patient. The average duration of symptoms in the patients with duodenal ulcer was eleven years.

A second group of patients were maintained on one form of therapy and studied at intervals by means of eight hour fractional gastric analyses. We wished to determine whether any sustained reduction in gastric acidity could be obtained by continued use of the Sippy or other forms of management.

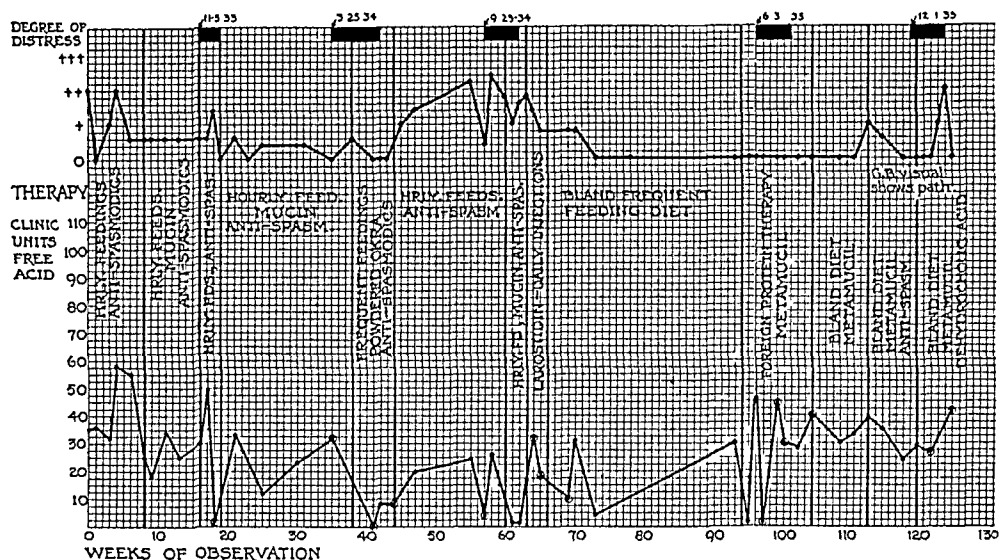


Chart 4—J S, a white man aged 43, had a typical history of ulcer. Chronic hypertrophic arthritis and chronic cholecystitis were complicating factors. This patient was studied for two years and five months. In November 1935 roentgenologic evidence of a pathologic condition of the gallbladder was obtained.

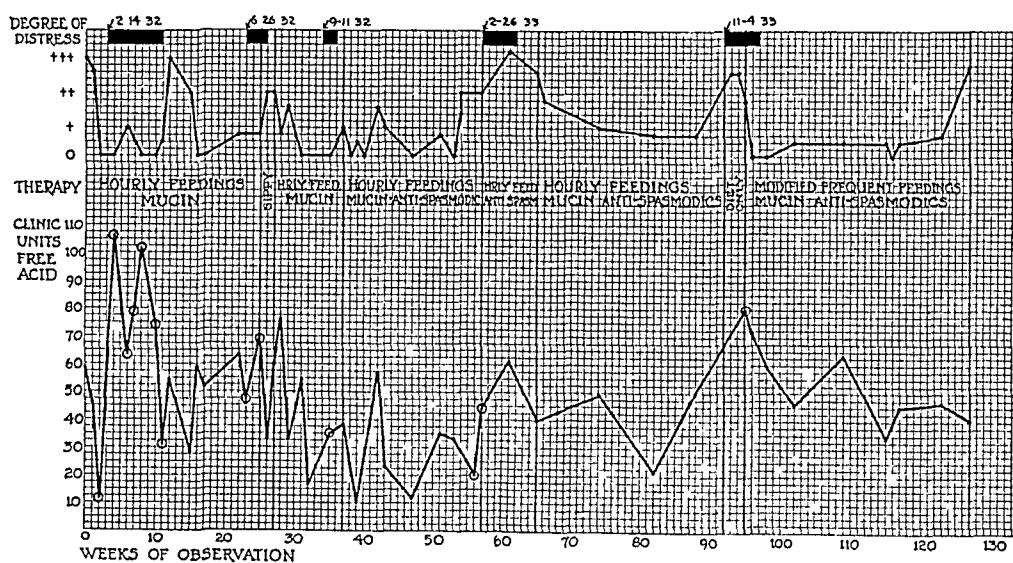


Chart 5—H C, a Negro aged 39, had a typical history of ulcer of seven years' duration. Previously he had been treated at several other clinics, with dietary management and alkaline powder. This patient was studied for two years and five months.

The routine Ewald test meal used in the analyses consisted of four crackers and two glasses of water. Aspiration of the stomach contents was performed after an interval of forty-five minutes. The stomach contents were analyzed for free, com-

bined and total acid and for blood by routine laboratory methods Previous to each test meal the patient had abstained from food, alkaline powders, mucin or any other medication for at least twelve hours

The criteria on which recurrences of the activity of the ulcer were based in his study were purely objective (1) the presence of blood in the gastric contents, (2) the presence of blood in the stools, (3) a marked increase in tenderness on abdominal palpation, (4) an increase in deformity roentgenologically and (5) an increase in the gastric retention occurring with increased spasm in the area of the ulcer

RESULTS

During the course of this study we were able to observe seventy-three recurrences of the activity of an ulcer The duration of the recurrences varied among the patients, likewise the intervals of

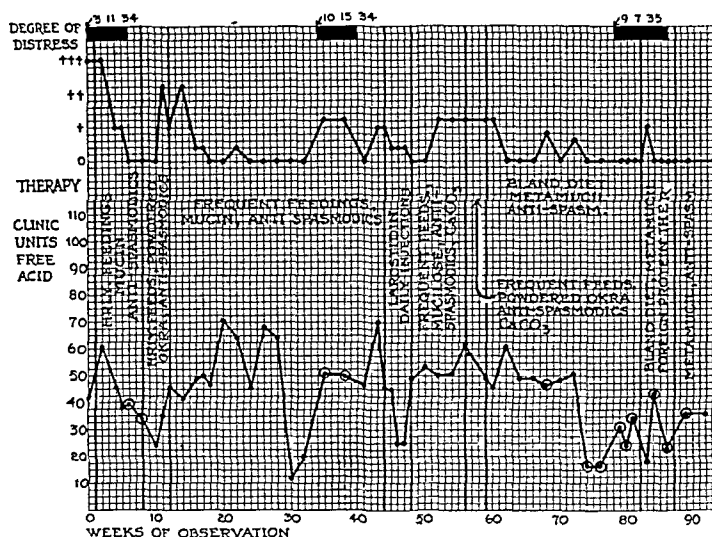


Chart 6—T C, a white man aged 47, had a typical history of ulcer He was first seen during an attack of pyelitis He was hospitalized during our observation for undulant fever, during which time he had a recurrence of ulcer Recurrences seemed to be associated with infections of the upper respiratory tract This patient was studied for one year and nine months Calcium carbonate was administered during two periods of study

quiescence between the flare-ups in activity Certain general observations, however, seem of interest Although some clinicians have previously commented on the apparent seasonal incidence of recurrences of ulcer, we have been unable to find figures on which the statements were based In our series 68.5 per cent of the seventy-three recurrences took place during the spring and fall The second general observation is the fact that in the majority of instances the recurrences followed the onset of an acute infection For the most part these infections involved the upper respiratory tract, but recurrences were also noted after an acute abscess of a tooth, a carbuncle and in one instance infec-

tion of the hand. In other patients emotional stress and strain seemed to be of greater significance as the predominant factor in bringing on the recurrence.

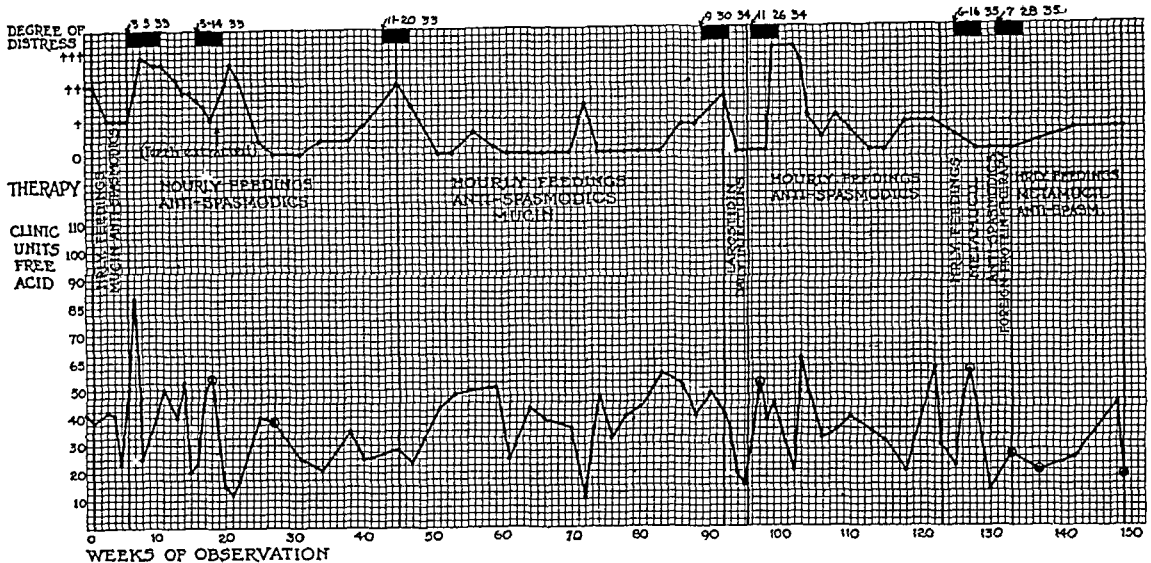


Chart 7—F L, a white man aged 46, had a typical history of ulcer, with prolonged use of alkaline powders prior to admission to the hospital. He showed marked emotional instability. This patient was studied for three years.

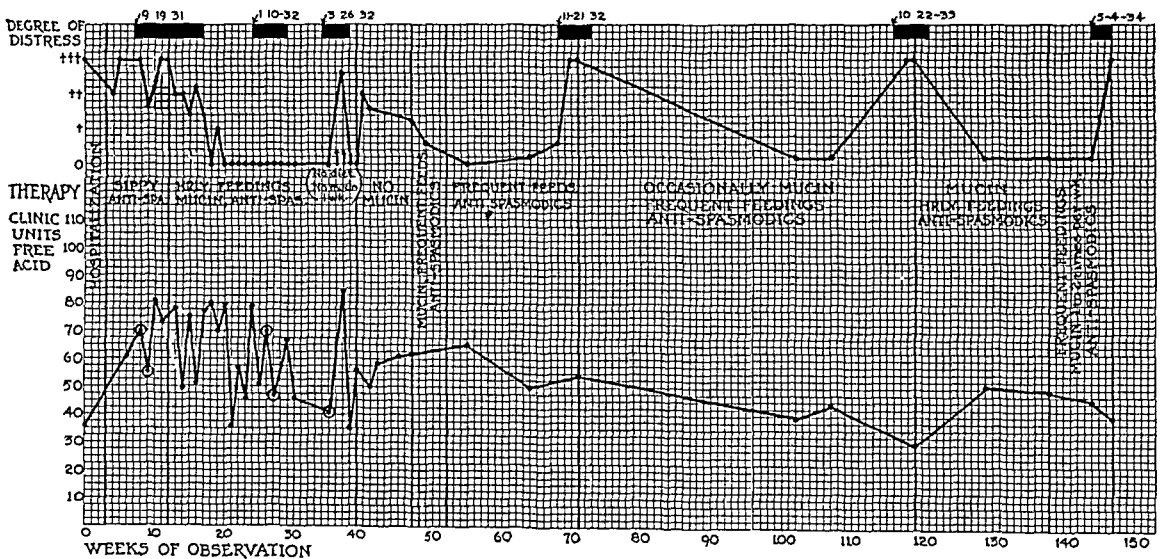


Chart 8—N H, a Negro aged 40, had a typical history of ulcer. Prior to admission to the hospital this patient had been hospitalized for management of ulcer for a total of one hundred and twelve days. He was studied for two years and eleven months.

The data demonstrate that the trend of gastric acidity bears no definite relationship to the onset of a recurrence. A rise in the level for free acid was observed prior to the recurrence of activity of the

ulcer in 46.5 per cent of the seventy-three recurrences. In 34.2 per cent, however, the values for acid were lower than the preceding levels, and in the remainder no significant change in acidity was observed. The chief point of interest is the fact that in the same patient the level of

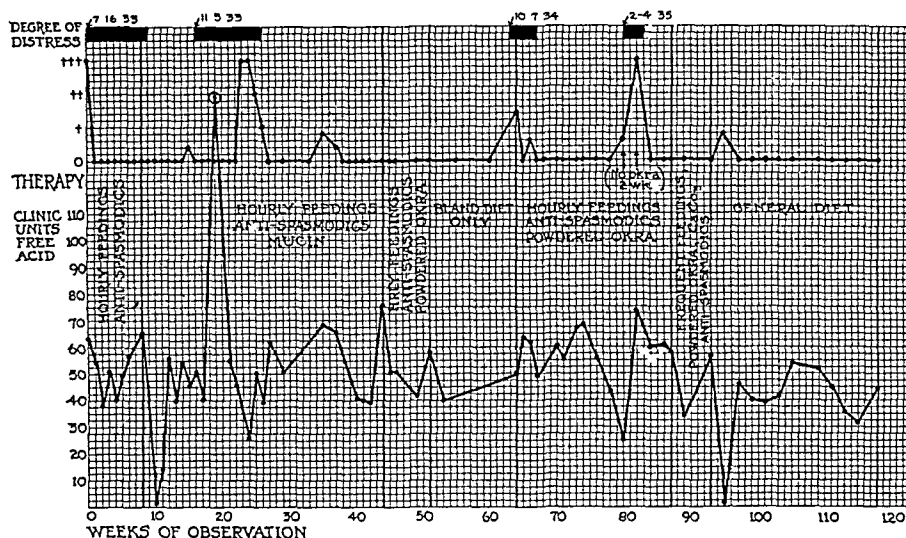


Chart 9—D H, a white man aged 47, had a typical history of ulcer. Two of the four recurrences were preceded by infection of the upper respiratory tract. Since January 1934 the patient had been working as a street laborer. He was studied for two years. In April and May 1935 calcium carbonate was administered.

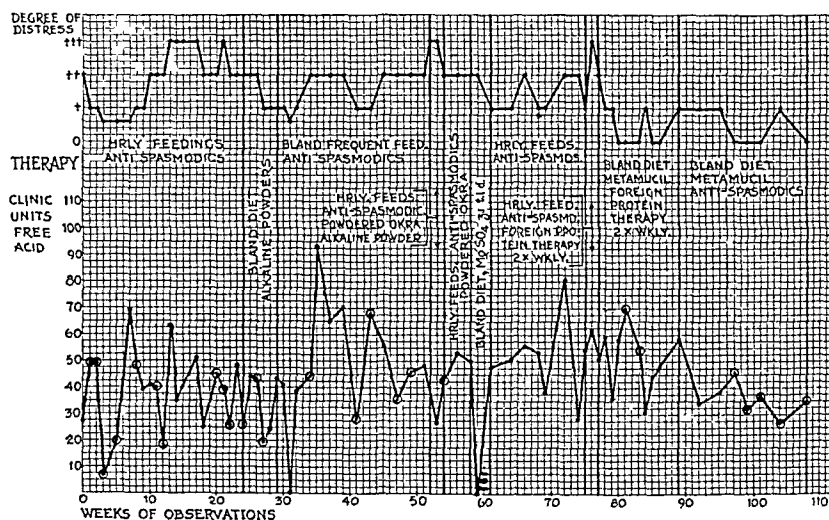


Chart 10—L A, a white man aged 48, was studied as a control. Thorough roentgenologic and laboratory studies revealed no basis for a diagnosis of duodenal ulcer. This patient had a so-called pseudo-ulcer syndrome. He was studied for two years and one month. From the fifty-ninth to the sixty-first week magnesium sulfate was administered, together with a bland diet.

free acid may rise, fall or undergo no alteration prior to a recurrence. Conversely, there were marked rises in the level of free acidity repeatedly without recurrence.

Similar fluctuations of the levels for gastric acid were observed during the periods of recurrence. The accompanying table shows the finding that in some patients the level for free acid falls during a recurrence. In other patients in a smaller number of instances there was a higher level for free acid during a recurrence than before it. In still others no significant change in free acidity was observed. Even for the same patient there was no constant behavior of the acid level during a recurrence. During one recurrence the acid level may be higher than its previous value, whereas in subsequent recurrences the

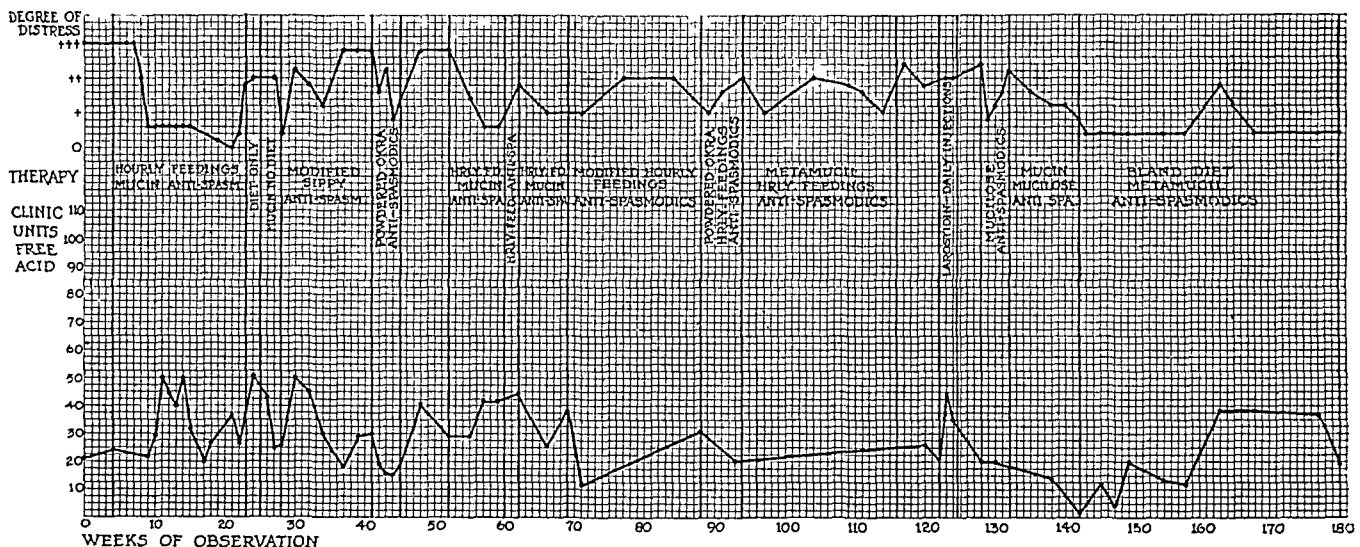


Chart 11—S B, a white man aged 32, was studied as a control. Thorough roentgenologic and laboratory studies revealed no basis for a diagnosis of duodenal ulcer. As with other patients in this group, this patient may be said to have shown a "pseudo-ulcer" syndrome. He was studied for three years and six months.

acid level may be lower or unchanged. The variations concerning each patient have been graphically arranged, examples being given in charts 1 to 9.

The level for free acid was found to bear no relation to the degree of distress manifested by the patients. In the intervals during which the patients experienced the greatest distress 50 per cent of the acid levels were lower than during intervals when no distress was present. The occurrence of distress, as indicated by the individual charts, was furthermore shown to bear little or no relationship to the activity of the ulcer in most instances.

It will be observed that for two patients (cases 5 and 9) on several occasions high values for free acid were obtained, but at the same time the patients were totally free from distress. In these instances distress did not appear until the free acid had dropped to within normal limits. In one patient (case 2) it will be observed that distress was present at intervals despite the existence of almost complete achlorhydria.

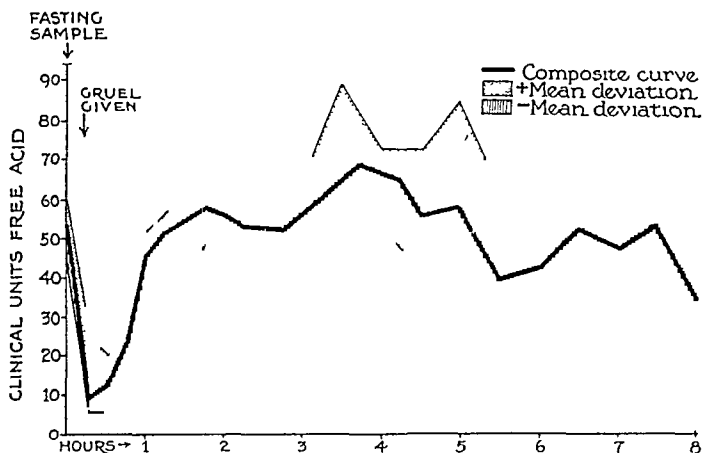


Chart 12—A composite curve for the results of eight fractional gastric analyses made for control patient H T. Nothing was administered during the test.

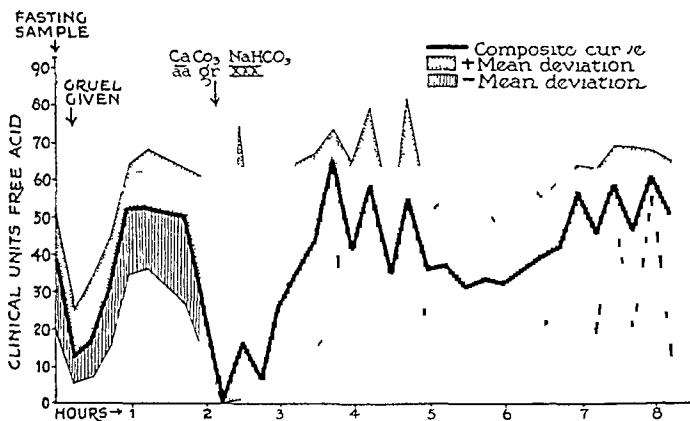


Chart 13—A composite curve for the results of seventeen fractional gastric analyses made for control patient H T after administration of alkali (calcium carbonate and sodium bicarbonate).

Owing to the persistently low level for free acid and the continued presence of blood in the gastric contents, this patient was examined roentgenologically at frequent intervals for malignant growth. The present excellent health of this patient, together with normal laboratory findings, eliminates the diagnosis not only of a gastric malignant growth but of pernicious anemia and gastric syphilis.

The two individual charts (charts 10 and 11) for the control group of five persons demonstrate the wide variations of the acid level in normal persons. Antacid therapy did not noticeably change the gastric acidity of these normal controls. From the standpoint of therapy it will be seen that in both the group of ulcer-bearing patients and the control series all measures have little effect in bringing about a sustained reduction of the levels for free acid in the fasting state. Fewer recurrences and best subjective results were obtained with continued dietary management, with frequent feeding plus mucin therapy.

Charts 12 and 13 illustrate the typical findings for the group of patients studied by means of fractional gastric analyses. This particular patient was maintained on hourly feedings and hourly powders throughout the period of observation. No medication or feeding was administered for twelve hours preceding each test. It will be observed that there was no significant reduction in the fasting level of free acid, despite the fact that alkalis had been stopped only twelve hours previously. It will also be observed that no sustained fall in the level for free acid resulted from the use of alkali. In no instance were we able to demonstrate a sustained lowering effect on the acid level due to neutralization therapy. Similar tests were also made with histamine, and no significant alteration in gastric behavior could be observed.

COMMENT

We are well aware that the advent of some of the more recent studies of gastric secretion by means of fractional methods of analysis, especially those of Klumpp and Bowie,¹² Martin and Becker,¹³ Fogelson¹⁴ and others, places the status of the accuracy of the routine Ewald procedure in some doubt. Comfort and Osterberg¹⁵ and Eusterman and Balfour¹⁶ still favor the Ewald procedure as a routine method of investigation and further maintain that its relative accuracy is high. The more detailed technical methods were impracticable in the present study because of the number of patients in the series and the long periods of observation. While the values reported for acid therefore

12 Klumpp, T. G., and Bowie, M. A. Studies on Gastric Secretion, *J. Clin. Investigation* **12** 1, 1933.

13 Martin, Paul, and Becker, K. P. Absolute Tests of Gastric Function as Basis for Comparing Amount and Acidity of Gastric Secretion, *Deutsches Arch. f. klin. Med.* **175** 1, 1933.

14 Fogelson, S. J. Personal communication to the authors, March 1936.

15 Comfort, M. W., and Osterberg, A. E. Gastric Secretion After Stimulation with Histamine in Presence of Various Types of Gastric and Duodenal Lesions, *J. A. M. A.* **97** 1141 (Oct 17) 1931.

16 Eusterman, G. B., and Balfour, D. C. The Stomach and Duodenum, Philadelphia, W. B. Saunders Company, 1935, p. 158.

may be subject to moderate error, according to some workers, the extended observation and the large number of analyses for each patient compensate for the variations of the single test meal

Indicating the degree of distress as well as the exact time and duration of the recurrences involved some difficulty. It is impossible to prove definitely whether or not a patient has an active ulcer, in spite of the conscientious use of the five criteria of diagnosis enumerated in a previous article.¹⁷ Blood in the gastric contents, blood in the stools and frequent roentgenologic studies proved to be the best evidence of recurrence. No reliance could be placed on the presence of hyperacidity. We believe that gross aid is obtained from roentgen studies, despite the fact that roentgenologists have become more cautious in their estimation of the activity of an ulcer. The history of the ulcer and the response to therapy were considered but have less than their usual value for patients with intractable ulcers.

Fowler, Spencer, Rehfuess and Hawk¹⁸ have shown that the stomach tends to bring its contents to a normal acid level regardless of the reaction of the ingested substance. Lockwood and Chamberlain,¹⁹ Crohn²⁰ and others have reported similar observations. Rehfuess and Hawk²¹ have reported that by means of fractional test methods they found evidence of the secretion of gastric juice of constant acidity in both normal and pathologic human subjects. While these investigations were carried on for brief intervals only, our data demonstrate that gastric acidity fluctuates from month to month and year to year without regard to therapy. Apparently the one constant feature is the fact that gastric acidity tends to moderate as the entire gastro-intestinal tract returns to normal.

Alvarez and Vanzant²² have previously indicated that in some persons the variations in gastric secretion are so wide that little value can

17 Brown, Clarence F. G., Cromer, S. P., Jenkinson, E. L., and Gilbert, N. C. Mucin Therapy for Peptic Ulcer, *J. A. M. A.* **99** 98 (July 9) 1932.

18 Fowler, C. C., Spencer, W. H., Rehfuess, M. E., and Hawk, P. B. Gastric Analysis. IV. The Gastric Equilibrium Zone, *J. A. M. A.* **77** 2118 (Dec. 31) 1921.

19 Lockwood, B. C., and Chamberlain, H. G. The Effect of Alkalis on Gastric Secretion and Motility as Measured by Fractional Gastric Analysis, *Arch. Int. Med.* **32** 74 (July) 1923.

20 Crohn, B. B. Effect of Antacid Medication on Gastric Secretion and Acidity, *Am. J. M. Sc.* **155** 801, 1918.

21 Rehfuess, M. E., and Hawk, P. B. Direct Evidence of the Secretion of Gastric Juice of Constant Acid Concentration by the Human Subject, *J. A. M. A.* **63** 2088 (Dec. 12) 1914.

22 Vanzant, F., and Alvarez, W. C. What Is the Value of Our Gastric Analysis? A Study of the Daily Variations in the Gastric Acidity of Two Normal Persons. *Proc. Staff Meet., Mayo Clin.* **6** 419 (July 15) 1931.

be attached to one test meal. The futility of a single test meal for diagnostic purposes is clearly demonstrated in our series of normal and ulcer-bearing persons.

The height of the acid level bears no relation to the degree of distress manifested by the patient on the basis of our findings. Any therapeutic procedure seems to produce temporary relief in some cases. We were unable to concu with Palmer's correlation between acid levels and the onset of distress. It appears therefore that the individual's inherent mechanisms of gastric defense control the levels of gastric acidity, and little can be done fundamentally by means of neutralization therapy.

We are now putting into practical use the concrete evidence of the frequency of recurrence during the spring and fall months. During these months patients with intractable ulcer under our observation are placed on careful dietary management, and gastric mucin is included as a prophylactic measure. In many instances this procedure seems effective. Thus far, however, the available data indicate that the seasonal frequency of recurrences of ulcer in patients with intractable ulcer has been definitely reduced.

CONCLUSIONS

There is no significant trend in the gastric acidity prior to a recurrence of activity of an ulcer. In the same patient the level for free acid may rise, fall or undergo no significant change before recurrence.

During a recurrence of activity, gastric acidity undergoes no constant variation. Upward or downward fluctuations occur in the same patient.

Definite evidence was obtained indicating a seasonal occurrence of activity of ulcers. Of seventy-three recurrences observed in this study, 68.5 per cent occurred during the spring and fall months.

The height of the level for free acid bears absolutely no relationship to the degree of distress manifested by the patient. Conversely, the acid levels were lower than the preceding levels 50 per cent of the time during occurrence of the greatest distress.

The degree of distress may in no way be a criterion of the activity of an ulcer. The patient may have every symptom of recurrence but have no ulcer. He may have no subjective symptoms and yet may have a highly active ulcer. Criteria of recurrence, therefore, must be objective, not subjective.

CENTRAL NERVOUS SYSTEM AND SUGAR METABOLISM

CLINICAL, PATHOLOGIC AND THEORETICAL CONSIDERATIONS, WITH
SPECIAL REFERENCE TO DIABETES MELLITUS

A R VONDERAHE, M D

CINCINNATI

Since the discovery of insulin the treatment of diabetes mellitus has made remarkable strides. Many factors underlying the causation of the disease, however, remain obscure. The associated anatomic changes are for the most part the result of an excess amount of sugar in the blood and are thus the effects rather than the causes of the disease. It is true that changes in the pancreas occur with great frequency, but these are not constant. In a study of 229 diabetic patients Warren^{1a} noted that the pancreas showed fibrosis, hyaline degeneration, hypertrophy, hydropic degeneration, pyknotic nuclei, hemorrhage or adenoma in the islands of Langerhans in 190 patients while in 69 patients it was normal. The author^{1b} stated

These cases in which changes in the pancreas are absent or too trifling to merit consideration have always puzzled and irritated the pathologist. It is difficult to conceive of long-continued and profound functional pathology without organic change, the field of mental disease excepted.

In explanation of these observations Warren^{1c} suggested three hypotheses

(1) The islands may be normal and insulin may be produced, but is either defective in quality or is neutralized by some substance in the body, (2) the diabetes may be of other than insular origin, and (3) the insulin may be formed normally by normal islands, but through failure in transport the insulin is not brought into the blood stream and so not distributed where its effects are needed.

Whichever (if any) one of these hypotheses is true, we must face the fact that cases of diabetes absolutely identical with one another from the clinical standpoint show no evidence of structural disease in the islands of Langerhans in one instance, and show marked injury of various types in still another.

Still more disturbing are this author's^{1d} observations on the pancreas of 200 nondiabetic persons. One or more of the changes previously noted for diabetes were observed in 67 (or 16.5 per cent) of this series of nondiabetic persons.

From the Department of Anatomy (Neurology), the University of Cincinnati Medical School

1 Warren, Shields. (a) *The Pathology of Diabetes Mellitus*, Philadelphia, Lea & Febiger, 1930, p. 42, (b) p. 198, (c) p. 53, (d) p. 72, (e) p. 194, (f) p. 196

The absence of pathologic changes in the pancreas has led to the suggestion that pituitary disease may be responsible for a certain number of cases. Marie,² in 1889, noted diabetes in 2 of 4 patients with acromegaly, while the association of glycosuria with tumor of the hypophysis was described by Loeb³ in 1898. Naunyn,⁴ in 1906, suggested that these tumors effected their results by pressure on a hypothetic "sugar center." Cushing⁵ reported a series of clinical observations and experiments pointing to the association of glycosuria with lesions of the pituitary body. Bailey and Bremer⁶ and others showed that these findings could be produced experimentally by means of lesions of the hypothalamus, the pituitary body, its nerve connections and the blood supply remaining intact. White⁷ and Joslin⁸ presented some evidence of relationship of diabetes and changes in the pituitary body by calling attention to the occurrence of diabetes among children who were taller than ordinary.

Warren¹⁰ studied the hypophyses of 27 diabetic patients who were free from stigmas of pituitary disease, and in none did he find significant variation from the normal. This observation tends to confirm the finding of Bailey and Bremer and others that the relationship of the pituitary body to diabetes is indirect, the primary metabolic center being in the hypothalamic area in close relation to the gland.

Observations by Cannon⁹ indicated that the emotions of rage and terror are productive of glycosuria. Clinical observations in the course of diabetes indicate a loss of sugar tolerance due to mental strain. The "sugar puncture" of Claude Bernard, again, points to a close relationship between the central nervous system and the pancreas. The intermittent action of the adrenal gland in these cases must be borne in mind. Beattie and his collaborators¹⁰ stated as their conclusion that the pos-

2 Marie, P. Acromegaly. A Clinical Study, *Progres med* **9** 189, 1889.

3 Loeb, M. The Pituitary Body in Diabetes Mellitus, *Zentralbl f inn Med* **19** 893, 1898.

4 Naunyn, B. Diabetes Mellitus, Vienna, A. Holder, 1906.

5 Cushing, H. The Pituitary Body and Its Disorders, Philadelphia, J. B. Lippincott Company, 1912.

6 Bailey, Percival, and Bremer, Frederick. Experimental Diabetes Insipidus, *Arch Int Med* **28** 773 (Dec.) 1921.

7 White, P. Potential Diabetic Child, *J A M A* **88** 170 (Jan 15) 1927.

8 Joslin, E. P. Treatment of Diabetes Mellitus, ed 4, Philadelphia, Lea & Febiger, 1928.

9 Cannon, W. B. Bodily Changes in Pain, Hunger, Fear and Rage, ed 2, New York, D. Appleton & Company, 1929.

10 Beattie, J., Brown, G. R., and Long, C. N. H. Physiological and Anatomical Evidence for Existence of Nerve Tracts Connecting Hypothalamus with Spinal Sympathetic Centers, *Proc Roy Soc, London, s B* **106** 253 (May 3) 1930.

terior hypothalamic nuclei influence sugar metabolism through their influence on the secretion of epinephrine. As far as the adrenal bodies are concerned in the production of diabetes, Warren¹² in a series of 300 autopsies observed no significant lesions in these glands.

That the nervous system plays a rôle in the alteration of sugar metabolism has been known for many years, particularly since Claude Bernard punctured the floor of the fourth ventricle and produced glycosuria. In the following case reports this effect is illustrated.

REPORT OF CASES

CASE 1—*Traumatic subarachnoid hemorrhage at base of brain, glycosuria*

A Negress aged 39 was admitted to the Cincinnati General Hospital in a state of unconsciousness after injury to the head. There was general muscular twitching. The deep reflexes were exaggerated. Urinary examination revealed an excessive amount of sugar. The patient died ten minutes after admission to

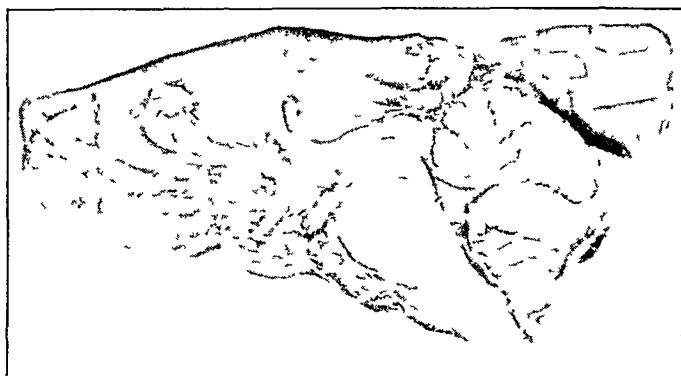


Fig 1 (case 1)—Extensive subarachnoid hemorrhage, with especially severe involvement of the tuber cinereum

the hospital. The history indicated that she had been in excellent health prior to the injury. A diagnosis of cerebral hemorrhage, probably traumatic, was made.

At autopsy an extensive subarachnoid hemorrhage was observed implicating all the structures at the base of the brain, including the tuber cinereum (fig 1). Gross and histologic examination of the pituitary gland showed no abnormality.

Comment—In this case there was evidence of the occurrence of a disturbance in sugar metabolism (glycosuria) in association with probable traumatic hemorrhage, implicating the tuber cinereum.

CASE 2—*Essential hypertension, hemorrhage into pons, with pressure effects on third ventricle, glycosuria*

A white woman aged 37 was examined in the outpatient dispensary of the Cincinnati General Hospital, and a diagnosis of essential hypertension was made. Several urinalyses made at various times showed no evidence of glycosuria. Subsequently the patient entered the hospital in a state of coma. The spinal fluid at the time was bloody. The urine showed an excessive amount of sugar.

At autopsy extensive hemorrhage was noted involving practically the whole substance of the pons, extending upward into the interpeduncular space and compressing the third ventricle (fig 2)

Comment—In this case there was evidence of a disturbance of the sugar-regulating mechanism from pressure effects on the hypothalamus or, more probably, from an interruption of the descending pathways from this area in the tegmentum of the pons



FIG 2 (case 2)—Hemorrhage involving the basal and tegmental portions of the pons, with rupture into the fourth ventricle



FIG 3 (case 3)—Hemorrhage into the midbrain, with extension into the pons

CASE 3—Cardiovascular renal disease, hemorrhage of midbrain, glycosuria

A 67 year old patient for several years attended the outpatient dispensary of the Cincinnati General Hospital because of hypertension. Repeated examinations of the urine showed no evidence of sugar at any time. After a "stroke of paralysis" the patient was brought to the hospital in a comatose state, presenting right hemiplegia. Urinalysis showed 4 + sugar. The patient died four days later.

At autopsy a hemorrhage was noted, having its origin in the left half of the midbrain and thrusting portions of the midbrain upward so as to compress the cavity of the third ventricle. Portions of the tegmentum of the midbrain and pons had been destroyed by the hemorrhage (fig 3).

Comment—The glycosuria in this case is regarded as due to compression of centers of carbohydrate metabolism in the hypothalamus or to destruction of the pathways from this area in the tegmentum of the midbrain

CASE 4—*Diabetes mellitus of increasing intensity, aphasia, psychosis, cyst of pulvinar of thalamus, obstructive internal hydrocephalus*

A white woman aged 63 at the time of entrance into the Hamilton County Chronic Disease Hospital presented slight mental confusion, aphasia, speech



Fig 4 (case 4) —The arrow indicates a cyst of the pulvinar of the thalamus which has grown mesially and caudally to erode the superior quadrigeminal body and to occlude the orifice of the aqueduct of Sylvius, producing internal hydrocephalus, which is especially marked in the third ventricle

defect, incontinence of urine, weakness of the legs and diabetes mellitus. In the course of two months the glycosuria increased in intensity in spite of the administration of insulin. The psychotic manifestations increased in severity. Several days before death occurred the pupils became like pinpoints and fixed, and other neurologic signs developed. Four months prior to the patient's death a diagnosis of mild diabetes mellitus was made by Dr Cecil Striker.

At autopsy a cyst of the pulvinar of the left thalamus was noted which had extended mesially and posteriorly to overlap and occlude the aqueduct of Sylvius, causing internal hydrocephalus, with marked dilatation of the third ventricle. On microscopic examination, in addition to other alterations, cell loss and retrograde changes were noted in the nucleus paraventricularis and in the substantia grisea of the hypothalamus (fig 4)

Comment—The origin of the diabetic state in this case may have been due to involvement of centers in the hypothalamus regulating sugar metabolism, or, if the cause existed elsewhere, the disease appeared to have been aggravated by pressure effects on this area

CASE 5—Chronic duodenal ulcer, excessive alcoholism, psychosis, bleeding into intestine, hyperglycemia

A Negress aged 40 was admitted to the Cincinnati General Hospital complaining of extreme pain and soreness in the abdomen. Two months prior to her admission to the hospital a diagnosis of duodenal ulcer had been made at the outpatient dispensary, at which time a specimen of urine had shown no sugar. There had been excessive alcoholism for three months and rather constant alcoholic indulgence for many years. During the last three weeks the patient's mental state had been regarded as disturbed. There was a general downward course, with increasing weakness as bleeding from the bowels continued. A specimen of blood taken on the day of the patient's death for chemical study contained 299 mg of sugar per hundred cubic centimeters.

At autopsy the diagnosis of a large duodenal ulcer was confirmed. Microscopic examination of the diencephalon revealed multiple hemorrhages in the anterior and superior aspects of the hypothalamus, implicating the superior portion of the nucleus paraventricularis. Multiple capillary hemorrhages were also present in the nucleus supra-opticus on both sides. There was marked destruction of many cells in the nucleus paraventricularis, and the remaining cells for the most part presented evidence of acute chromatolysis and other retrograde changes. There was appreciable cell loss in the substantia grisea of the third ventricle and in the nucleus tuberculi lateralis, and throughout the entire gray matter of this area there was increased glial proliferation (fig 5)

Comment—This patient presented terminal hyperglycemia associated with recent capillary hemorrhages in the anterior portion of the hypothalamus implicating most prominently the nucleus paraventricularis

RÔLE OF THE CENTRAL NERVOUS SYSTEM IN THE REGULATION OF SUGAR METABOLISM—A HYPOTHESIS

Recently Morgan, Malone and I¹¹ studied cellular changes in the hypothalamus of 15 patients with diabetes mellitus, using as controls the

11 Morgan, L. O., Vonderahe, A. R., and Malone, E. F. Pathological Changes in the Hypothalamus in Diabetes Mellitus, *J. Nerv. & Ment. Dis.* 85:125, 1937

brains of 5 nondiabetic patients for whom the causes of death were as follows (1) malignant hypertension, (2) septicemia, (3) gunshot wound in the back, (4) pulmonary tuberculosis and (5) mercury bichloride poisoning. The results of this study indicated a constant loss of cells, ranging from 30 to 65 per cent, in the nucleus paraventricularis in all the patients with diabetes. In the remaining cells of this

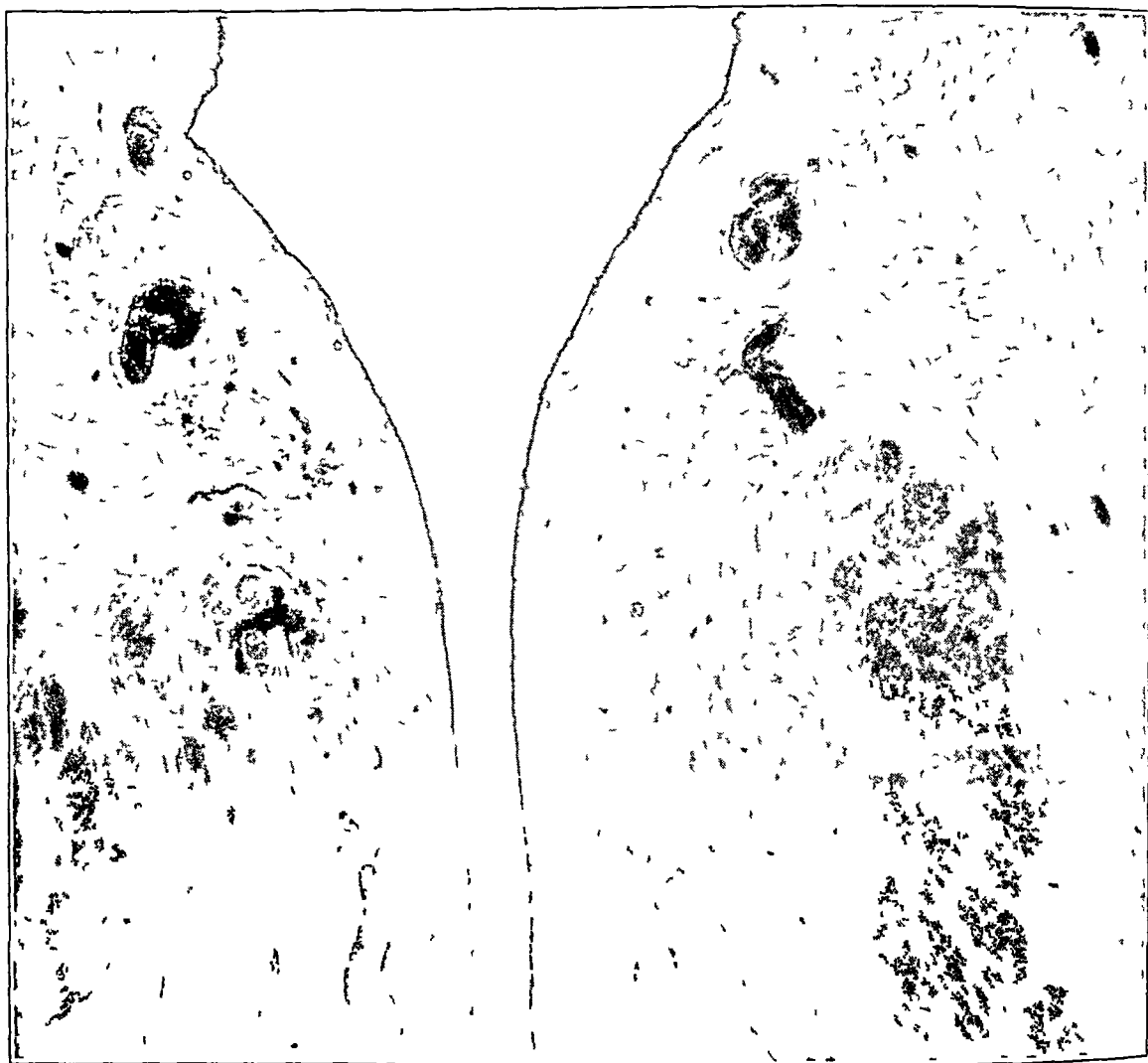


Fig 5 (case 5)—Multiple venous hemorrhages with smaller capillary and arteriolar hemorrhages may be noted in the superior anterior portion of the hypothalamus between the ependyma and the fornix and implicating the nucleus paraventricularis. Morgan's stain, $\times 25$.

nucleus marked retrograde changes tended to occur. In 6 of the 15 patients there was, in addition to the aforementioned changes, severe cell loss in the substantia grisea of the third ventricle and in the nucleus tuberis lateralis associated with a considerable amount of retrograde

change in the remaining cells of these nuclei. In the latter group of patients a psychosis was associated with the diabetes mellitus, this finding corresponds to that noted in the previous work of Morgan and Gregory,¹² in which cell loss in the nucleus tuberis lateralis and in the substantia grisea of the third ventricle was observed in a group of 32 psychotic patients presenting in common the presence of mental deterioration. With a single exception, the changes in the diabetic patients were much milder than those in the deteriorated psychotic patients.

Utilizing these data and those obtained from the patients in the present series it is possible to construct a working hypothesis for a phase of the regulation of sugar metabolism by the central nervous

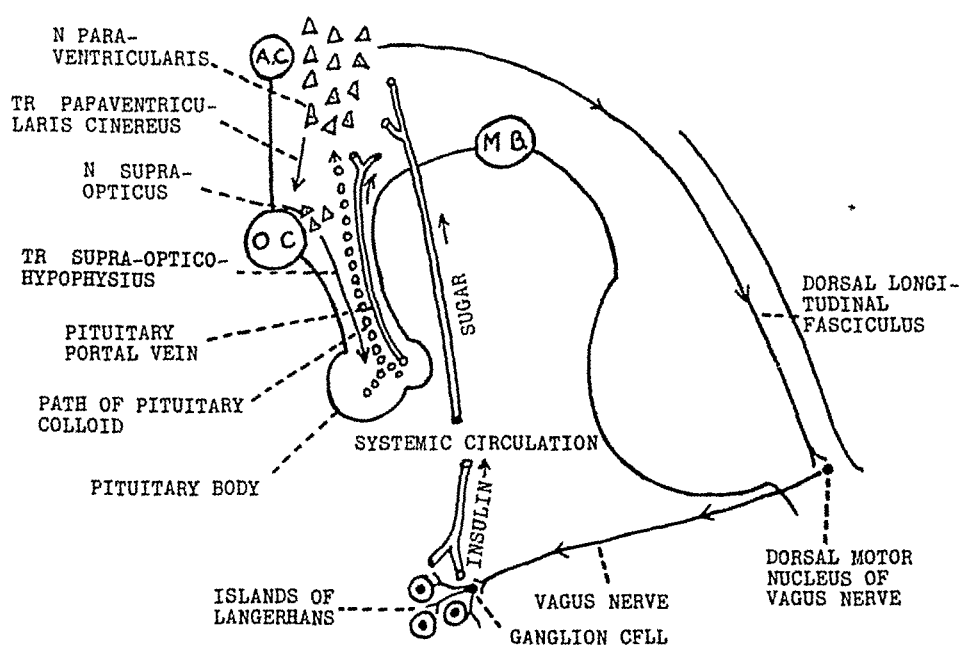


Fig 6—Diagram explaining the rôle of the nucleus paraventricularis of the hypothalamus in the regulation of sugar metabolism *AC* indicates the anterior commissure, *OC*, the optic chiasm, and *MB*, the mammillary body The pathways for the stimulation of insulin by way of the thoracolumbar sympathetic system, with the probable superior center in the posterior portion of the hypothalamus, are not indicated in the diagram Further explanation is given in the text

system (fig 6). One may recall that the nucleus paraventricularis is connected by fiber paths to the nucleus supra-opticus, which in turn is connected by fiber paths to the posterior lobe of the pituitary body. Again, the pituitary body sends some of its secretion directly into the hypothalamus (Collin¹³), and some of the secretion may be carried

12 Morgan, L O, and Gregory, H S Pathological Changes in the Tuber Cinereum in a Group of Psychoses, J Nerv & Ment Dis **82** 286, 1935

13 Collin, Remy The Functional Relationship Between the Pituitary Body and the Tuber Centers, *Ann de méd* **18** 428, 1925

to the hypothalamic nuclei through a system of portal veins (Popa and Fielding¹⁴ and Basir¹⁵) Also, there is the possibility that nerve fibers run from the pituitary body to the hypothalamic nuclei There is an intimate connection, accordingly, between the nucleus paraventricularis and the pituitary body Fibers leaving the nucleus paraventricularis pass downward close to the wall of the ventricles in the dorsal longitudinal fasciculus, or bundle of Schutz, to terminate about cells in the dorsal motor nucleus of the vagus nerve Preganglionic fibers stream from this nucleus to ganglion cells in the pancreas From here short postganglionic fibers form networks around the islands of Langerhans (peri-insular network of Gentes) and terminate in a wealth of minute fibrils on the island cells¹⁶ Gentes¹⁷ emphasized the richness of these plexuses on island cells and stated that it distinguishes them from the cells of the pancreatic gland proper Pensa¹⁸ confirmed these observations

The hypothesis proposed here regards the nucleus paraventricularis as a central stimulator of the production of insulin The preceding work suggests that in addition to being stimulated by neural impulses, the cells of this nucleus are stimulated also by the presence of sugar, just as the neurons constituting the respiratory center are stimulated by the presence of carbon dioxide It is assumed that an excess of sugar in the blood activates these cells, resulting in the sending of impulses to the islands of Langerhans over the pathways described, thereby causing an increased production of insulin The insulin causes a lowering in the sugar content of the blood, and the paraventricular nucleus comes to rest If an excess of blood sugar from any cause continues, the syndrome of diabetes mellitus is produced, the paraventricular nucleus then is overworked, its cell bodies show evidence of fatigue and they finally die so that cell counts indicate a significant loss in number

From an anatomic standpoint the pituitary body appears to be capable of influencing carbohydrate metabolism not only by the effect of its internal secretion in the blood but by the direct effects of its secretion on the cell groups in the hypothalamus It is likely that the

14 Popa, G, and Fielding, U The Vascular Link Between the Pituitary and the Hypothalamus, *Lancet* **2** 238 (Aug 2) 1930, The Portal Circulation from the Pituitary to the Hypothalamic Region, *J Anat* **65** 88, 1930

15 Basir, M A The Vascular Supply of the Pituitary Body in the Dog, *J Anat* **66** 387, 1932

16 Greving, R, in Muller, L R *Lebensnerven und Lebenstrieb*, Berlin, Julius Springer, 1931, p 112

17 Gentes, B Note on the Nerve Terminations in the Islands of Langerhans, *Compt rend Soc de biol* **54** 202, 1902

18 Pensa, A Observation on the Description of Blood Vessels and Nerves to the Pancreas, *Internat Monatschr f Anat u Physiol* **22** 90, 1905

effect of the pituitary body on the nucleus paraventricularis is inhibitory, with the result that excessive pituitary secretions may repress the production of insulin and cause a rise in the sugar content of the blood. Conversely, interference with the influence of the pituitary body may activate the production of insulin. Thus, Davis, Cleveland and Ingram¹⁹ found that lesions properly placed in the hypothalamus would ameliorate the symptoms of pancreatic diabetes and prevent the glycosuria and hyperglycemia produced by stimulation of the superior cervical ganglion.

As noted previously, the islands of Langerhans receive, in addition to the fibers from the vagus nerve, postganglionic fibers from the thoracolumbar sympathetic system. Beattie and others have shown that the posterior hypothalamic cell groups are concerned with sympathetic effects. The conversion of glycogen into sugar and the increased production of insulin with the sympathetic emotions anger and rage have been demonstrated by Cannon.⁹ This function, associated as it is with strenuous emotion or with severe exertion, is by nature of short duration or even of infrequent occurrence, while the effect of the parasympathetic (vagal) system is by nature anabolic and relatively constant in action.

The hypothesis proposed here recognizes that alterations of sugar metabolism may be caused in various ways, one of which is a disturbance in the central nervous system, by regarding the physiology of carbohydrate metabolism as a cycle in which the nervous system is one factor it provides for *effects* in the nervous system of continued hyperglycemia and so affords an explanation of numerous clinical phenomena of diabetes mellitus. It is not inconsistent with any rôle that the pituitary body, adrenal gland or any other internal secreting gland may play in the disorder.

In conclusion, it is important to point out that the effect of the nervous system is one of *modifying* certain intrinsic physiologic and chemical reactions which constitute essential sugar metabolism. That the internal glands, too, act merely in modifying this intrinsic mechanism is strikingly illustrated by the Houssay dogs, in which sugar metabolism proceeds more normally again when, after the removal of the pancreas, the pituitary body also is removed.

19 Davis, L., Cleveland, D., and Ingram, W. R. Carbohydrate Metabolism. The Effect of Hypothalamic Lesions and Stimulation of the Autonomic Nervous System, *Arch Neurol & Psychiat* **33** 592 (March) 1935. Cleveland, D., and Davis, L. Further Studies on the Effect of Hypothalamic Lesions upon Carbohydrate Metabolism, *Brain* **59** 459, 1936.

SUMMARY

The proper understanding of diabetes mellitus as a clinical entity requires the inclusion of the central nervous system. Available evidence does not justify a view that diabetes mellitus is invariably caused by a lesion of the central nervous system. But clinical and pathologic data indicate that the nervous system becomes an integral factor in the cycle of events which constitute the phenomena of this disease. A hypothesis is proposed which assumes that the nucleus paraventricularis in the hypothalamus is stimulated by the presence of sugar to activate the cells of the islands of Langerhans to the production of insulin, and an analogy is suggested between this mechanism and the stimulation of the cells of the respiratory center by carbon dioxide. This hypothesis has been applied to patients with diabetes mellitus without gross cerebral lesions and to patients with various lesions of the brain, confirmed at autopsy, and presenting in common hyperglycemia or glycosuria.

Progress in Internal Medicine

GASTRO-ENTEROLOGY IN 1936

SELECTED TOPICS

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Instead of attempting to cover the whole field of gastro-enterology for 1936, I have selected four topics of major importance for review for this year. All deal with the stomach. The first is gastroscopy. It demands attention not only as a diagnostic procedure but because it is making possible a better understanding of many conditions affecting the gastric mucosa which have not been fully appreciated previously. The second is gastritis. The renewed interest in this disease has come about largely through the facility with which the gastric mucous membrane may now be directly observed through the flexible gastroscope. The third is the histidine treatment of peptic ulcer. This new therapeutic procedure for a long-recognized clinical condition was reviewed two years ago, while in its infancy. The large number of articles on this subject which have appeared in all parts of the world since then make possible now a more mature judgment of the efficacy of a form of treatment which sprang from an extremely flimsy experimental basis. The fourth concerns the experimental production of gastric erosions (ulcers) by means of a deficient diet and the prevention of the occurrence of the lesions by the supplying of certain dietary substances. This subject has as yet received no attention in medical research but in my opinion offers a fertile new line of investigation of certain gastric disorders.

GASTROSCOPY

The rigid gastroscope has been in use since the last century. Many drawbacks have prevented its general application to the study of gastric disease. Within the last few years a flexible gastroscope has been developed, which may be readily passed and which gives a really excellent view of the interior of the stomach. For the detailed technic of gastroscopic examination the original articles should be consulted. The method and the advantages to be derived therefrom have occupied the attention of a number of observers during the past year.

In a rather long but interesting discussion of gastroscopy Kalpen¹ traces the history of its development from "the wish" of Hippocrates to its fulfilment in the perfection of a flexible gastroscope in 1932 by

¹ Kalpen, E. Zur Licht und Instrumententechnik in der Gastroskopie, Mitt. a. d. Grenzgeb. d. Med. u. Chir. **44** 157, 1936.

Wolf and Schindler. A fundamental problem in gastroscopy as well as in all forms of endoscopy has been the development of proper illumination. The solution of this problem, along with many other technical difficulties, is given in some detail, together with a number of illustrative figures.

Kerkhof² describes gastroscopy as another method of examining the stomach. He states that it is not a distressing examination for the patient, and as far as the gastroscopist is concerned it is not a difficult procedure. He would "much rather pass a gastroscope than a stomach tube." For all practical purposes gastroscopy is without danger. One patient with an early cancer on the posterior wall of the stomach near the greater curvature was successfully operated on when roentgen examination twice gave negative results although a lesion was definitely recognized through the gastroscope. Grossly the lesion appeared benign, but the microscopic examination proved it to be malignant.

The indications and contraindications for gastroscopy and the technic of the procedure are described by Symonds³. Contraindications are either extrinsic, such as aortic aneurysm, enlargement of the thymus or some other mediastinal tumor and disease of the spine interfering with its mobility, or intrinsic, such as advanced organic disease, extensive varicosities of the esophagus and acute esophagitis. The indication for gastroscopy is any persistent or unexplained symptom referable to the stomach. Of special interest are all forms of gastritis, gastric symptoms with negative roentgen findings, gastric neurosis, unexplained gastrointestinal hemorrhage, peptic ulcer and gastric cancer, particularly when the differential diagnosis between the last two is involved. The technic is outlined in detail.

Chevalier L. Jackson⁴ describes the procedure of gastroscopy with the flexible gastroscope. He concludes that this instrument marks a new era in the endoscopic study of the stomach and that every "good gastroenterologist" will make gastroscopy a part of the routine study of his patients. However, he considers the use of the flexible instrument only an addition to the use of the rigid instrument when in the hands of the peroral endoscopic specialist.

Schindler⁵ also describes the examination of the stomach with a flexible gastroscope and presents its advantages. This report is of particular interest because of the author's ingenuity in developing this instrument. The discussion is well worth reading.

2 Kerkhof, A. Gastroscopy, Another Way of Examining the Stomach, *Minnesota Med* **19** 647, 1936.

3 Symonds, C. W. Gastroscopy. Indications, Contraindications, Technic, *Arch Phys Therapy* **17** 574, 1936.

4 Jackson, C. L. Gastroscopy with the Flexible Gastroscope, *Ann Otol Rhin & Laryng* **44** 1150, 1935.

5 Schindler, R. Gastroscopy with a Flexible Gastroscope, *Am J Digest Dis & Nutrition* **2** 656, 1936.

A consideration of the present status of gastroscopy from many points of view is presented by Schloss⁶ He describes the procedure as the intravital inspection of the gastric mucosa by nonoperative means and points out its clinical advantages over other well established methods The history of gastroscopy clearly shows that the development of the flexible gastroscope has led to its use as a routine in many of the hospital clinics abroad and that it is rapidly coming into favor in this country The new instrument and its method of introduction are well described and illustrated The technic of its passage is comparatively simple, and gastroscopy is now readily performed in the outpatient clinic The number of contraindications to this form of examination are small, with disease of the esophagus standing out as the chief obstacle to the procedure The clinical results are given in some detail Although the evidence obtained is subject to errors of individual interpretation, it may be of definite diagnostic and therapeutic value in a number of diseases of the stomach To epitomize the clinical potentialities of this objective method in comparison with roentgenographic studies, it may be said that gastroscopy is superior when the pathologic process is widespread and superficial and that roentgen examination is superior when well localized, pronounced lesions are present Gastroscopic examination should precede an operation on the stomach Its scientific potentialities are great, as it is adding much useful information regarding the progress in treatment and classification of intragastric disease

The use of the flexible gastroscope is well exemplified by Carey⁷ He records a number of instances in which the gastroscopic findings indicated the correct diagnosis when other methods of examination either revealed no abnormality or were in error It is particularly important to prove the presence of gastritis if it is suspected either alone or in conjunction with some other lesion of the stomach or of the duodenum

"The introduction of gastroscopy into the field of diagnosis and research marks one of the truly great advances in the realm of gastroenterology," Boros states⁸ His observations are based on 100 cases, and in only 6 of these was the procedure unsuccessful He has found that the quantity of gastric juice secreted in response to a test breakfast has no relation to the occurrence of inflammatory manifestations in the gastric mucosa The presence or absence of gastric acidity does not in itself predicate the existence of inflammation, and normal acidity may be present in a diseased stomach He has found by endoscopic means that there are marked gastric changes in diseases affecting the biliary tract and that the diagnosis of gastritis belongs entirely within the realm

6 Schloss, J Gastroscopy, *Internat Clin* **4** 1, 1936

7 Carey, J B The Use of the Flexible Gastroscope, *Minnesota Med* **19** 652, 1936

8 Boros, E Gastroscopy Observation in One Hundred Cases, *Am J Digest Dis & Nutrition* **3** 533, 1936

of the gastroscope Gastroscopy's applicability includes the group of cases in which the diagnosis is obscure and further investigation is indicated

In an article entitled "Gastroscopic Observation Concerned with the Gross Anatomy of the Stomach The Musculus Sphincter Antri, Observation of the Position of the Stomach, the Mucosal Folds," Schindler⁹ compares his gastroscopic findings with those of the anatomist, the physiologist and the roentgenologist Many of his findings do not coincide with those obtained by other methods Any physician proposing to use a gastroscope should read this article in its entirety

The gastroscopic findings in grave vomiting of pregnancy seem to explain adequately the mechanism of this troublesome condition Chevallier and Pigeaud¹⁰ have long recognized that this type of vomiting is accompanied with pronounced blanching of the gastric mucosa Recently in 3 cases they were also able to make out that there is pronounced atony of the gastric fundus, with persistent hypertonicity and spasm of the pyloric sphincter and the pylorus muscle The spasm may be permanent during the period of observation, or there may be occasional brief periods of relaxation These observations adequately explain why neither liquids nor solids can be maintained in the stomach and why the introduction of a tube into the duodenum is so important in the treatment of vomiting of pregnancy

The value of gastroscopy in correlating the presence of gastritis in a number of disorders of the skin and its etiologic relationship with these disorders is well borne out in a series of three reports by Chevallier and Moutier¹¹ They emphasize the importance of subjecting a patient with chronic urticaria, eczema or one of certain other dermatoses to direct observation of the gastric mucosa by means of the gastroscope

Phytobezoars are rare, but the roentgenographic appearance of the tumor in the stomach is usually characteristic Moersch and Walters¹² report the first case of this condition in which the bezoar has been visualized and recognized preoperatively by means of gastroscopy Gastric symptoms followed a persimmon "spree," and ultimately gastrotomy revealed a rocklike tumor, approximately 7.5 by 10 cm Direct gastroscopic observation of the tumor may be of value as an added diagnostic procedure

9 Schindler, R Gastroscopic Observation Concerned with the Gross Anatomy of the Stomach The Musculus Sphincter Antri, Observations of the Position of the Stomach, the Mucosal Folds, *Am J Digest Dis & Nutrition* **3** 149, 1936

10 Chevallier, R, and Pigeaud, H Les renseignements fournis par la gastroscopie dans les vomissements graves de la gestation, *Lyon med* **157** 562, 1936

11 Chevallier, P, and Moutier, F L'estomac des eczémateux, *Arch d mal de l'app digestif* **26** 75, 1936, L'estomac des urticariens, *ibid* **26** 83, 1936, Les localisations gastriques spécifiques des dermatoses, *ibid* **26** 87, 1936

12 Moersch, H J, and Walters, W Phytobezoar with Visualization by Means of Gastroscopy, *Am J Digest Dis & Nutrition* **3** 15, 1936

The relation of gastritis to the formation of peptic ulcers has attracted wide attention. One school of thought claims that gastritis leads to ulceration and that the two conditions are essentially the same disease. The other school claims that they are independent diseases. Chevallier¹³ is of the latter school and relies on gastroscopy to prove his contention. He reports 2 cases of gastric ulcer, giving illustrations of the endoscopic findings and also of the resected specimens. In 1 case there was perulcerous gastritis, but in the other no gastritis existed. Gastroscopic examination should precede operation for peptic ulcer to determine the extent of gastritis, if present, as a wider dissection is indicated when there is a surrounding area of localized inflammation.

The pyloric obstruction observed in adults who are free from peptic ulcer and from carcinoma is usually considered to be due to benign hypertrophy of the pyloric musculature. That this is not always true is clearly brought out in a case reported by Chevallier,¹⁴ in which gastroscopy supplied important diagnostic information which has heretofore been lacking when this problem has been encountered. The patient had pernicious anemia of severe degree. Gastroscopy revealed diffuse atrophy of the mucosa of the body of the stomach and diffuse tumefying edema of all the mucosa of the pyloric region. Subsequent roentgen examination revealed the amputation of the pyloric antrum that is usually considered typical of a gastric malignant growth. The anemia cleared up with liver therapy, and the pseudocancerous tumor disappeared completely. Without surgical exploration the exact knowledge of the nature of this phantom tumor could be obtained only by its direct inspection through the gastroscope.

Another somewhat similar case is reported by Cordier and Chevallier¹⁵. In this instance there was a transient tumor of the pylorus, which appeared and disappeared and when present gave roentgen findings suggesting a neoplasm. Gastroscopy revealed the true nature of this condition. There was an area of sharply localized edema of the mucosa of the pyloric region, reaching its maximum median to the anterior pillar and thereby completely obscuring the pyloric orifice. The rest of the gastric mucosa was free from abnormal changes. Apparently this phantom tumor may be classed as an allergic phenomenon similar to the recurrent localized forms of edema described by Quincke. The presence of these mucosal lesions has often been suspected in the group of conditions described as visceral erythema, and direct observation of the

13 Chevallier, R. La gastrite péri-ulcéreuse, *J de med de Lyon* **17** 73, 1936.

14 Chevallier, R. Un nouveau cas de pseudo-cancer pylorique au cours d'une anémie de Biermer, diagnostic gastroscopique, *Lyon med* **157** 218, 1936.

15 Cordier, V, and Chevallier, R. Un cas d'oedeme fugace antro-pylorique pseudo-tumoral, aspects radiographiques et gastroscopiques, *Lyon med* **157** 384, 1936.

gastric mucosa through the gastroscope now makes possible the verification of these suspicions, at least as far as the stomach may be involved

Benedict,¹⁶ of Boston, has had wide experience in studying gastric cancer through the gastroscope. He observes that gastroscopy is important in selected cases of neoplasm of the stomach in order to make possible the early diagnosis of carcinoma of the stomach, in differentiating benign from malignant lesions, in determining the location and extent of the lesion and in excluding intra-gastric pathologic conditions. Pratt¹⁷ urges the use of the gastroscope in conjunction with the Gruskin test to further earlier diagnosis of cancer of the stomach. An important use of gastroscopy is to follow the effect of treatment on gastric lesions. Arloing, Morel, Josserand and Chevallier¹⁸ report 6 cases of gastric cancer in which they directly observed a diminution in the area of tumor infiltration coincident with intravenous therapy with "ferriscorbones" (combinations of dehydroxycevitamic acid and iron and other metals). The value of their observations lies in the method employed to control their studies rather than in any therapeutic results produced.

Schindler,¹⁹ who more than any other person is responsible for the recent development of gastroscopy and the knowledge of the gastric mucosa accruing thereby, reports on the clinical value of gastroscopic examination of the stomach. The procedure with the flexible gastroscope is simple and safe and permits visualization of the greater part of the stomach. The two real difficulties are, first, orientation in the large gastric cavity and, second, the interpretation of observations. In order to overcome these difficulties one must have an extensive knowledge of the normal gastric mucosa and also a wide experience with all its abnormalities. Slight pathologic changes may be overlooked, which is not of great practical importance, but, worse, perfectly normal variations may be interpreted as the effects of disease. Ulcers of the duodenum and pyloric channel are not visible through the gastroscope, and prepyloric ulcers are rarely, if ever, seen. Pyloric obstruction observed roentgenographically is benign if no tumor mass is directly visible and if the pylorus cannot be observed because of distortion from prepyloric adhesions. Ulcers of the angulus and lesser curvature are generally well seen, although they may not be visualized roentgeno-

16 Benedict, E. B. Gastroscopic Observations of Neoplasm, *New England J. Med.* **214** 563, 1936.

17 Pratt, G. H. Diagnosis of Cancer of the Stomach. The Use of the Gastroscope and the Gruskin Test, *Arch. Surg.* **33** 138 (July) 1936.

18 Arloing, F., Morel, A., Josserand, A., and Chevallier, R. Action desinfiltrante des injections intra-veineuses de ferriscorbones sur six cas de cancer gastrique sous contrôle du gastroscope, *Lyon med.* **157** 333, 1936.

19 Schindler, R. On the Clinical Value of Gastroscopy, *Proc. Staff Meet., Mayo Clin.* **2** 747, 1936.

graphically. However, in some cases an ulcer which is readily outlined on roentgen examination cannot be located through the gastroscope. Antium gastritis, which is said to accompany peptic ulcer, has not been observed, hypertrophic ulcerative gastritis of the body of the stomach is frequent. Superficial gastritis is common, but ordinarily it heals. It may develop into chronic atrophic gastritis, usually with anacidity. A completely atrophic gastric mucosa may regenerate with liver therapy. Chronic hypertrophic gastritis is an important clinical entity in which healing does not occur. It is found around gastric ulcers. Chronic gastritis is the most common postoperative disease of the stomach and is severe. The diagnosis of a localized carcinoma may be made by a glance at the gastric wall. A number of patients for whom the diagnosis was made early have survived operations for three, five or even ten years. The operability of gastric carcinoma can be decided on by gastrosocopy and gastroscopy alone, and only when the condition is known to be operable should surgical intervention be employed. It is suggested that each patient with atrophic gastritis or with a benign epithelial tumor, both forerunners of carcinoma, should be examined twice yearly by gastrosocopy and the roentgen relief method.

The development of the flexible gastroscope has led to its use in intragastric photography. Goyena, Islenghi and Hofmann,²⁰ of Argentina, review the development of this subject and describe in detail the gastrophotor of Heilpern. This flexible photographic unit carries two cameras capable of taking sixteen simultaneous exposures of the gastric mucosa. Changing the position of the gastrophotor makes possible a practically complete photographic record of the mucosa of the entire stomach. The position of the unit is controlled by fluoroscopic examination. When this is satisfactory the stomach is dilated with air. Then automatically the objectives of the cameras are uncovered, and at the same time the electrical contact is made, giving an intense intragastric illumination. The exposures occur just at the time the walls of the stomach are about to contract. In this gastrophotor the difficulties of the older forms of apparatus are apparently overcome. The instrument can be passed easily and safely, and complete permanent records can be obtained of gastric lesions.

GASTRITIS

Until recently the diagnosis of gastritis was all too often a cloak for ignorance. It was used to cover almost any type of acute or chronic indigestion when the cause of the symptoms was obscure. When the diagnosis was correct it was based rather on inference than on fact. The glib pronouncement of yesterday that a patient was suffering from gastritis is in the same category with the oft repeated diagnosis of

²⁰ Goyena, J. R., Islenghi, J. P., and Hofmann, H. Gastrophotography, *Rev Gastroenterol* 3 158, 1936.

"intestinal influenza" of today With the advent of improved histologic studies of the gastric mucosa and particularly with the advent of the flexible gastroscope, gastritis is gradually being brought out into the light and is better understood today than ever before The advancement in knowledge of this condition and how much yet remains which is ill understood may be judged from the following abstracts

Schindler and Ortmayer²¹ present their classification of chronic gastritis, based on 1,200 gastroscopic examinations The histologic methods leading to an anatomic classification are unsatisfactory, owing to a lack of knowledge of the effect of ligatures on the vessels when specimens of gastric tissue are obtained by surgical resection Three forms of gastritis—the hypertrophic, the atrophic and the mixed—have been clearly demarcated by the pathologist, but it is not proved that they cannot appear in an otherwise normal stomach Also, these findings frequently are present in a patient without any gastric symptoms The authors prefer to consider that the mucous membrane of the adult who has no symptoms is normal

Gastroscopic examination is a direct method of examining the gastric mucous membrane Even the deeper-lying lesions can be observed, as the mucosa is transparent Gastritis is characterized by changes associated with swelling, exudation or atrophy, although atrophy may be degenerative, as in pernicious anemia Observations have been made in 346 cases of the chronic form of gastritis About 50 per cent of the gastroscopic studies show these changes Chronic benign ulcer is not included in the description of chronic gastritis Repeated observations in the same case are essential to an understanding of the course of gastritis and are essential to correct classification Four types of gastritis are recognized by the direct method of examination (1) superficial, (2) atrophic, (3) hypertrophic and (4) that following operations on the stomach They differ as to gastroscopic picture, course and prognosis

In superficial gastritis the surface epithelium is cloudy and may be spotted, edematous, superficially eroded and slightly hemorrhagic Adherent glairy secretion is a feature These changes are most marked in the body of the stomach and usually are absent from the antrum With careful control of the diet and lavage this disease disappears completely In atrophic gastritis the mucous membrane loses its normal orange-red color and becomes gray and transparent, the underlying blood vessels may be visible This condition usually remains stationary but may rarely develop into diffuse general atrophy Normalcy is not regained, but the patient suffers little The superficial form may develop into the atrophic, and this can occur rapidly In hypertrophic gastritis

²¹ Schindler, R., and Ortmayer, M. Classification of Chronic Gastritis with Special Reference to the Gastroscopic Method, *Arch Int Med* **57** 959 (May) 1936

the chief finding is swelling of the mucosa, which may result in pseudo-polyposis. Hemorrhage is often extreme, multiple erosions come and go and ulceration may occur. All these changes are much more frequent in the corpus than in the antrum. The term *gastritis chronica hypertrophicans ulcerosa* is applicable. None of the author's patients with this serious disease have regained complete health, but atrophic gastritis develops rarely. In postoperative gastritis the prognosis is poor, as in even the superficial forms there is no tendency to heal. An etiologic classification of gastritis, although desirable, is not at present possible, owing to a lack of knowledge of the causes. Symptoms, laboratory findings and roentgen observations may be helpful but are of little or no diagnostic value compared with gastroscopic observations, particularly serial observations.

At the Brussels International Congress for Gastro-Enterology, Zweig,²² of Vienna, reviewed completely the present status of chronic gastritis. In his opinion medical interest in peptic ulcer and functional disturbances of the stomach had almost submerged the clinical diagnosis of chronic gastritis until most recently. The classification of exogenous and endogenous gastritis is still serviceable. Gastritis and ulcer are always associated, although their causal relationship is as yet undetermined. Many authors believe that the incidence of gastritis in adults with ulcer is 100 per cent. It reaches a peak in patients between 40 and 50 years of age and falls off markedly in older patients. Symptomatically low or no acidity and excess of mucus are the important symptoms, combined with the gastroscopic picture of chronic catarrh and hypertrophy or atrophy of the gastric mucosa. Roentgen findings are valuable. Treatment consists of (1) a bland diet, (2) medications, the nature of which vary with the presence or absence of free acidity, (3) local treatment, such as irrigations, (4) *Tinkkunen*—the ingestion of large amounts of alkaline waters, and (5) surgical treatment in cases of severe and intractable gastritis.

Mahlo²³ presents some original ideas on the relationship between the formation of gastritis and the gastric mucus. The mucus has many important functions, such as protection of the mucosa, absorption of hydrochloric acid to counteract alkalis and ferments, reactivation of ferments and protection of vitamin C. It is a complex substance composed of albumin, carbohydrate and mucosulfuric acid. It has the function both of absorbing and of chemically binding hydrochloric acid. Injurious alterations in the mucus may be brought about both by an effect on the secreted mucus and by injury to the mucus-secreting cells. The commonest cause of gastritis is alcohol, which produces more or less

²² Zweig, W. Die chronische Gastritis, *Wien klin Wchnschr* **48** 1535, 1935.

²³ Mahlo, A. Beziehungen zwischen der Entstehung der Gastritis und dem Magenschleim, *Deutsche med Wchnschr* **62** 1216, 1936.

marked changes in the mucus, depending on its concentration. The absorptive capacity of the mucus is interfered with, and histamine is set free, influencing the production of hydrochloric acid and water. A failure of mucus protection to mucosal epithelium results and vasodilatation occurs. A peptic ulcer may arise in such an area of localized gastritis. The "vital resistance" of the tissues often prevents this sequence of events.

Other common exogenous causes of gastritis are acetylsalicylic acid and nicotine. With normal values for acid in the stomach, the mucus will have maximum absorption of hydrochloric acid, and none of the acetylsalicylic acid will be absorbed. Absorption will take place in case of subacidity or anacidity, and irritation of the gastric epithelium will result. Nicotine is not absorbed by either acid or alkaline gastric mucus and cannot have a direct effect on the lining epithelium of the stomach. It is absorbed in other organs and exerts its effect in the stomach through the splanchnic nervous system. The localized gastritis accompanying gastric carcinoma, the author believes is due to the action of a special ferment selective for epithelial tissues. The protective mechanism is increased production of mucus. The author states that he once inadvertently swallowed some of this ferment, causing gastritis for three weeks, and although he had never had any gastric disturbance previously, he has had distress occasionally ever since this unfortunate episode. It is evident that localized gastritis, like ulcers, has no single cause.

Although in gastritis there is characteristically an excess secretion of mucus, when ulcers are present there is often less mucus than normally, so that the lesion is not well protected. Injections of histidine may be beneficial in this type of disorder by increasing the production of mucus. As mucus is digested in the duodenum and amino-acids, such as histidine, are set free, a diminished production of mucus means a diminished production of histidine. The beneficial effects of mucin administered orally or of histidine administered parenterally may be due to the greater quantity of histidine introduced, making possible an increased secretion of mucus. Clinical experience supports these suppositions.

Darling²⁴ presents a compact and up-to-date review of chronic gastritis in the *Medical Journal of Australia*. He emphasizes that achlorhydria may be only symptomatic and may exist without any anatomic change in the gastric mucosa. Carnot and Gaehlinger²⁵ review gastritis in *Paris médical*, emphasizing the greater perfection in diagnostic investigations which exist today.

24 Darling, H. C. R. Chronic Gastritis, *M. J. Australia* 2 45, 1936.

25 Carnot, P., and Gaehlinger, H. La pathologie digestive en 1936, *Paris med* 1 273, 1936.

Hurst²⁶ also reviews the subject of gastritis. He particularly stresses that it is likely to develop in patients with constitutional hyperchlorhydria or with hypochlorhydria or achlorhydria, because of a lack of secretion of protective mucus. It not only predisposes to such intrinsic diseases of the stomach as peptic ulcer and carcinoma but is responsible for such extrinsic disorders as disturbances in hematopoiesis and disorders in the nervous system.

One of the series of articles on treatment in general practice in the *British Medical Journal*, which was written by S. W. Patterson,²⁷ is on gastritis. As his classification and treatment of this condition are of the old textbook variety, this paper is mentioned only to illustrate how long it takes new and accepted concepts of a disorder to reach the general practitioner. If "faulty table habits" and a "lack in pleasant surroundings" during meals are truly causes of chronic gastritis, as the author states, surely most Americans should suffer from this disease.

Pevsner and Gordon²⁸ believe that the clinical aspects of chronic gastritis have not been sufficiently studied. On the basis of a detailed study of 500 cases they recognize two general groups: one in which gastritis is a concomitant of some other disease and one which is basically a clinical entity with a definite clinical picture. This picture may vary, depending on whether there is deficient gastric secretion or normal or excessive secretion. Achylia may be responsible for serious manifestations outside the stomach, such as those which occur in some of the anemias and in nutritional allergy. Hypersecretion is associated with neuro-endocrine and psychotic types of disturbances. One type of secretory disturbance may merge into the other, the two being accompanied with similar changes in motility noted roentgenographically. Chemical analysis of gastric secretion and roentgen studies of the gastric mucosa by the relief method give accurate information as to the course of the inflammatory lesion. Dietary treatment is the fundamental form of therapy in chronic gastritis and must vary with the amount of gastric secretion and the degree of inflammation. The neurohumoral influence must be taken into consideration.

Eusterman²⁹ discusses the problem of gastritis and reports 10 histologically verified cases. Although only two serious diseases of the stomach—cancer and peptic ulcer—are usually considered in cases in which gastric disorders are manifest and although healthy skepticism has been maintained toward gastritis, this disorder must now be con-

26 Hurst, A. F. Gastritis, *Arch. f. Verdauungskr.* **58** 121, 1935.

27 Patterson, S. W. Treatment of Acute and Chronic Gastritis, *Brit. M. J.* **1** 272, 1936.

28 Pevsner, M., and Gordon, O. Clinique et diétothérapie des gastrites chroniques, *Acta med. Scandinav.* **88** 278, 1936.

29 Eusterman, G. B. The Gastritis Problem. Notes on Histologically Verified Cases, *South. M. J.* **29** 684, 1936.

sidered of frequent occurrence. Inflammation commonly causes symptoms in many other organs, and it should not be surprising that recent investigations prove this to be true in the stomach. However, there is no close correlation between the symptoms and the presence or degree of inflammation. Furthermore, the impression is given that the enthusiastic gastroscopist finds some abnormality of the gastric mucosa in the majority of cases. The diagnosis must be guarded as to the relation of gastritis and the patient's complaint, and pathologic confirmation is of the utmost value. Classification, symptomatology and treatment are dealt with in some detail.

After a description of the histologic picture of the normal gastric mucosa, Baker,³⁰ of the Mayo Clinic, describes the changes occurring in chronic gastritis. Part or all of the mucosa may be involved. In cases of not far advanced gastritis there is observed an increase in stroma tissue and in lymphocytes which may form germinal centers. In cases of more advanced gastritis, atrophy of the specific epithelial cells occurs, hyperplasia may take place or these cells may present the picture of intestinal epithelium. The muscularis mucosae is always involved, with thickening due to both hypertrophy and fibrosis of the muscle tissue. Erosion or ulceration of the mucosa may take place.

Konjetzny³¹ believes that the diagnosis of gastroduodenitis is based on a definite pathologic picture with clearcut clinical findings. Histologic studies prove that there is acute and more or less pronounced erosive gastroduodenitis when the "ulcer syndrome" is noted but no ulcer is present. The pyloric syndrome, pyloritis, pylorospasm, hyperesthesia of the stomach and irritability of the stomach are less exact terms for the same pathologic condition. On purely clinical grounds it is not possible to differentiate between gastroduodenitis and gastric and duodenal ulcers. Treatment belongs to the realm of internal medicine and not of surgery. Even organic pyloric stenosis is often due to edema associated with the inflammation, and improvement can readily be demonstrated roentgenographically from eight to ten days after the start of dietary, antacid and atropine treatment. Surgical treatment is to be deplored under these circumstances. Hypertrophic pyloric stenosis and pyloric carcinoma must not be confused with gastroduodenitis, as their treatment is operative.

Swalm, Jackson and Morrison,³² of Philadelphia, have attempted to correlate the clinical and gastroscopic findings in a series of cases of

30 Baker, C. P. Histopathology of Chronic Gastritis, Proc. Staff Meet., Mayo Clin. **11** 521, 1936.

31 Konjetzny, G. E. Das Krankheitsbild der Gastro-Duodenitis, Med. Klin. **32** 473, 1936.

32 Swalm, W. A., Jackson, C., and Morrison, I. Correlation of Clinical and Gastroscopic Findings in Chronic Gastritis with Report of Cases, Rev. Gastroenterol. **3** 219, 1936.

chronic gastritis. They point out that there is no definite correlation between histologic abnormalities of the gastric mucosa and disturbances of gastric secretion, although at times hyperacidity may be associated with antral gastritis and subacidity with fundal gastritis. However, changes in secretion are often dependent on variations in the function of the nervous system. The important point of the relation of gastritis to peptic ulcer seems to have been cleared up by accurate histologic studies and by skilled gastroscopic observations. Gastritis almost invariably accompanies ulceration. The cytologic study of the gastric sediment should not be neglected, as it is a valuable index of inflammatory changes.

These authors carried out gastroscopic examination 196 times in 135 cases, and gastritis of various types was revealed in 35 per cent of the cases. Their criteria for diagnosis are recorded in detail. In 9 of 10 cases of peptic ulcer there was definite gastritis. In all but 1 of 13 cases of hypertrophic gastritis there was normal or high acidity, and in this 1 case the condition was associated with a gastric malignant growth. In all 9 of the cases of atrophic gastritis there was low or no acidity. In other mixed groups there were no constant secretory changes. It is evident that proliferative hypertrophic gastritis may be the forerunner of peptic ulcer, as its association with hyperchlorhydria is the usual finding. Seven cases of hypochlormic achlorhydric anemia are described, atrophic gastritis being present in each case.

These authors have not found roentgenographic relief study of the mucosal pattern to be an aid in the diagnosis of gastritis when checked by gastroscopic studies, and they feel that many conditions clinically suggesting peptic ulcer are really gastroduodenitis.

Leotta,³³ of the University of Palermo, feels that gastritis occurs in all sorts of intra-abdominal diseases, not alone with peptic ulcer or cancer of the stomach. It is a predecessor of gastroduodenal ulcer, but there is no sharp dividing line between chronic gastritis without ulceration and that with ulceration. In the latter type the inflammation is prolonged, with marked formation of scar tissue. A case of localized hypertrophic gastritis is reported from Brazil by Cotrim.³⁴ Clinically and roentgenologically the condition appeared to be gastric carcinoma, but operation disclosed a benign lesion of an inflammatory nature.

Despite the extensive studies of gastric physiology during the last century, knowledge of gastric functions is far from complete. However, a new doctrine has recently come to light—that the stomach occupies a

33 Leotta, N. Gastrite cronica ed ulcera gastro-duodenale, *Riforma med* 51 1823, 1935.

34 Cotrim, E. A proposito da hypertrophia localizada da mucosa gastrica simulando carcinoma, *Ann paulist de med e cir* 31 501, 1936.

place of prime importance in functions of the blood. Guillaume³⁵ notes that in addition to the well known external gastric secretions and the pyloric hormonal secretion stimulating the glands of the fundus, there is also a hormonal principle regulating hematopoiesis. This substance is found in the liver and is deficient in severe hepatic disease, such as advanced cirrhosis or acute yellow atrophy. It is not a product of the hepatic parenchyma but is stored there, awaiting the demands of the blood-forming organs. In the absence of this hormone, the production of blood cells returns to the embryonal type, and pernicious anemia results. Achylia is the rule in this form of anemia, and the basis of its development is degenerative gastritis, which is frequently accompanied with stomatitis, glossitis and intestinal disturbances.

Gastritis with achlorhydria or hypochlorhydria is also associated with hypochromic microcytic anemia, which may be considered the inverse of pernicious anemia. Diffuse atrophic gastritis is constantly observed gastroscopically in the course of this type of anemia and may be present in the nonanemic stages. The presence of glossitis simply indicates that there is gastritis. Histologically, the gastric mucosa may be purely atrophic or may show hypertrophic atrophy. It is probable that achylia, atrophy and anemia are coordinate and dependent manifestations, but it is as yet difficult to correlate clinical symptoms with them as they are so often symptomless in themselves. Certainly they frequently occur without an absence of the hormonal secretion stimulating hematopoiesis.

A group of French investigators³⁶ have studied the relation of atrophic gastritis to the course of alcoholic polyneuritis and have considered the clinical, chemical and gastroscopic aspects of this problem in 50 cases. Dyspeptic symptoms are constant and precede those of involvement of the nervous system by weeks or even months. In 33 cases achlorhydria occurred after the injection of histamine, and hypochlorhydria was marked in 12 cases. Early in the course of the disorder gastroscopy showed atrophic gastritis, and when the gastric mucosa was observed during the first two months and before the onset of the neuritis, gastritis was a constant finding. However, later, although the evidence of neuritis persisted, gastroscopic examination might show a normal picture. It is evident that gastric inflammation precedes the development of the neural lesions and may clear up before those lesions do.

In a discussion of precancerous gastritis Moutier³⁷ states that gastritis does not produce cancer but provides the soil on which cancer

35 Guillaume, A. C. Etude physiopathologique sur le rôle hématopoïétique de l'estomac, *Arch d mal de l'app digestif* **26** 241, 1936.

36 Villaret, M., Moutier, F., Justin-Besançon, L., and Klotz, H. P. Caractère spécial des troubles gastriques au cours de la polynevrinite alcoolique, *Bull et mém Soc méd d hóp de Paris* **52** 1155, 1936.

37 Moutier, F. La gastrite précancéreuse, *Paris med* **1** 283, 1936.

develops Peptic ulcers associated with gastritis are not concentrated anatomically in the same areas in which cancer develops and are not a cause in themselves of cancer The clinical courses of gastritis and early carcinoma of the stomach may merge, making any definite differentiation impossible Apogastitis, gastritis accompanied with manifestations elsewhere in the body, for instance, in the skin, blood or nervous system, does not produce an increased incidence of gastric malignant disorders, nor do the disorders associated with various forms of anemia Ignorance of the nature of cancer is still too great to permit relating the cause directly to gastritis

The relation of gastritis to carcinoma of the stomach has been analyzed from pathologic material by Tuomikoski³⁸ In a study of 158 resected specimens he noted pangastritis in 77 per cent, antral gastritis in 22 per cent and no gastritis in only 2 cases That atrophic gastritis is the primary predisposing disease is indicated by the following facts 1 The localized and generalized forms are morphologically similar 2 The characteristic changes of chronic gastritis are no more marked near the tumor than at a distance from it 3 The incidence and intensity of these changes are independent of the nature of the tumor 4 There is evidence that the changes in the gastric mucosa have taken a long time to develop The author concludes that in most cases gastric carcinoma probably arises on a basis of chronic atrophic gastritis

Attention is called to the association of gastritis with urticaria by Chevallier and Moutier³⁹ They studied 24 cases of urticaria relative to the digestive origin of the disorder They made a gastroscopic examination in 20 cases, and the diagnosis of gastritis was established on the gastroscopic evidence In half the cases there was gastritis, which was of the atrophic variety in 8 instances The majority of the patients had achlorhydria While it is evident that the cause of urticaria is not necessarily directly digestive in origin, they feel that atrophic gastritis with achlorhydria was the rule in too large a group of cases to be coincidental The importance of this association was strengthened by the fact that in 8 cases the condition was greatly improved or cleared up entirely when large doses of iron were given, while 4 patients with normal gastric mucosa and normal gastric secretion failed to respond to iron An analogy exists between the excellent response of patients with chlorotic anemia and atrophic gastritis and that of patients with chronic urticaria and the same gastric defect Certain French authors⁴⁰ report on a carefully studied case of gastritis with

38 Tuomikoski, V Gastritis and Carcinoma, *Acta chir Scandinav* **78** 251, 1936

39 Chevallier, P, and Moutier, F Les urticaires avec gastrite atrophique, *Ann de dermat et syph* **7** 337, 1936

40 Gate, J, Thiers, H, Chevallier, R, and Michell, P J A propos des modifications gastriques dans l'eczéma, *Lyon méd* **158** 130, 1936

achlorhydria and erythrodermic eczema. The cutaneous lesions were unaffected by a number of treatments until iron was administered, when they markedly improved and pruritus disappeared.

Gastritis has been described in rats fed a diet deficient in vitamin B₁. Hemorrhagic erosions and chronic ulcers are also said to occur. Simpson,⁴¹ not satisfied with the methods employed in producing these lesions, carried out similar experiments in which he rapidly excluded vitamin B₁ from the diet. Certain microscopic changes developed deep in the gastric mucosa, but there was no evidence of atrophic erosions or ulcerations. These changes following complete deprivation of vitamin B₁ can be of little if any importance in the genesis of gastric ulcer.

HISTIDINE TREATMENT OF PEPTIC ULCER

No new form of therapy in the last decade has received such universal attention and enthusiastic acclaim as the histidine treatment of peptic ulcer. A survey of the current literature makes the reasons for this obvious but also shows the gradual development of a healthy skepticism not only concerning the alleged brilliant results of the treatment but as to the soundness of the few basic experiments which have led to the erection of this therapeutic colossus. Only time and conservative judgment can determine the place that injections of histidine will ultimately occupy in the list of procedures available to combat a disease which has long withstood all panaceas.

A single enthusiastic report of a case by Davis,⁴² of Australia, illustrates the remarkably early improvement which may occur in some persons with chronic duodenal ulcer while receiving histamine therapy. In less than three weeks Davis' patient not only was entirely relieved of symptoms but was able to partake of "cold collation, salad, trifle with alcohol in it, and other sweets, and he crowned his indulgence with a large glass of beer and a good nobbler of whisky" without suffering any ill effects. In a careful study of 3 cases Finnegan and Elward⁴³ noted marked clinical improvement in each. All symptoms, including pain, completely disappeared by the third day of treatment, and the patients were able to return to their usual mixed meat and vegetable diet. Mastronardi and Bagnasco⁴⁴ report 12 cases from the Argentine. In 9 not only did pain cease, but there was a satisfactory improvement in

41 Simpson, C. K. Observations upon Gastritis, *Guy's Hosp. Rep.* **86** 120, 1936.

42 Davis, K. J. B. Treatment of Chronic Duodenal Ulcer with Histidine, *M. J. Australia* **1** 172, 1936.

43 Finnegan, J. F., and Elward, J. F. Histidine Treatment of Peptic Ulcer. Report of Three Cases, *M. Ann. District of Columbia* **5** 135, 1936.

44 Mastronardi, V., and Bagnasco, F. Contribucion al estudio aplicacion de la histidina en las ulceras gastro-duodenales, *Rev. Asoc. med. argent.* **50** 955, 1936.

weight and in the number of red blood cells. The course of injections was repeated in 7 instances in an effort to avoid recurrences. Eighteen cases of uncomplicated peptic ulcer treated with histidine are reported from London by Love⁴⁵. Complete relief and disappearance of roentgen evidence of ulceration were obtained in half the cases.

Voigt⁴⁶ notes that the efficacy of a form of therapy may be better judged from a few carefully described observations than from statistics. He reports 2 cases of gastric ulcer, including roentgenograms, which illustrate the remarkable healing effect occurring during treatment with histidine. In both cases the ulcers were very large and penetrating, and in both cases they healed completely, although lesions of this type rarely respond to the usual forms of therapy. The author believes the treatment in these 2 cases was a crucial test for treatment with histidine and that the biologic value of the therapy is proved. In a brief review in the *Gazette des hôpitaux* recommending the use of histidine in the treatment of gastroduodenal ulcers, Quénée⁴⁷ advises follow-up therapy of two series of six daily injections a year. In this way the impositions of a strict diet may be avoided.

As a follow-up study of a previously reported series of 21 cases, Valini and McLaughlin⁴⁸ publish their findings in 73 cases of peptic ulcer in which the patients were treated with histidine and observed over a period of six months. The patients were ambulatory, usually were on a liberal diet and were not given alkalis. Seven of them suffered from gastric ulcers, the rest, from duodenal ulcers. For ten days they received daily intramuscular injections of 5 cc of a 4 per cent solution of levohistidine monohydrochloride in an isotonic medium. If the symptoms were not relieved by then, from two to four times the dose was given daily. The length of the daily treatment varied from ten to sixty days, depending on how soon the alleviation of symptoms occurred, then one or two injections a week for one or two months more were deemed advisable. The authors suggest no indications for the necessity of repeating a course of treatment. These injections were without danger to the patient. Gastric analysis showed a tendency of acidity to be reduced to normal. In 80 per cent of the cases the patient gained weight. The immediate results as to subjective complaints showed complete relief after twenty-four injections in all but 14 cases, and in 3 of these subsequently there was entire relief. This group included

45 Love, R. J. M. Histidine Treatment of Peptic Ulcer, *Brit. M. J.* **1** 582, 1936.

46 Voigt, W. Ueber Erfolge mit der Histidinbehandlung der Ulkuskrankheit, *Deutsche med. Wchnschr.* **62** 1218, 1936.

47 Quénée, N. Un traitement classique des ulcères gastroduodénaux à l'histidine, *Gaz. d. hop.* **109** 668, 1936.

48 Valini, I. F., and McLaughlin, R. F. The Histidine Monohydrochloride Therapy of Gastroduodenal Ulcer, *Illinois M. J.* **69** 39, 1936.

6 of 7 cases of gastric ulcer All disappearance of the roentgenographic evidence of ulceration occurred in only 37 per cent One patient with a previously intractable duodenal ulcer was completely relieved by the injections, but perforation occurred two weeks later (I have had a similar experience) The authors make the observation that patients with syphilis do not respond well to this form of treatment They conclude "This amino acid treatment in our series, as far as the time-factor permits of comparison, has proved much more satisfactory than the various modes of accepted ulcer therapy"

The problem of the effect of histidine on the healing of peptic ulcers has been approached in a direct way by Korbsch⁴⁹ With an experience based on gastroscopy performed about 5,000 times, he has applied the knowledge thus obtained to observing the changes occurring in ulcerating lesions of the gastric mucosa during and after injections of solution of levohistidine monohydrochloride Serial observations in about 30 cases have enabled him to draw certain conclusions which are well substantiated by thirty-six sketches of the lesions His conception of the development and course of peptic ulcer must be understood before the results of the studies are considered

Korbsch states that in his observation of hundreds of ulcers, gastritis has never been lacking and that it is the conditioning process which permits ulceration to appear Also, the resistance of the gastric mucosa is dependent on vitamins, and if there is vitamin deficiency, gastritis and ulceration will occur In some instances only the administration of vitamins will restore the stomach to normalcy Three types or stages of ulceration are observed, and they have a direct bearing on the roentgen findings and response to treatment The flat ulcer of the mucous membrane gives no positive roentgen signs and tends either to heal spontaneously or to respond rapidly to a diet rich in vitamins Deeper penetration of such an ulcer, with the development of indurated edges, involves the underlying nerve plexus, causing localized paralysis of the wall of the stomach and an outpocketing of the wall, recognized roentgenographically as the characteristic ulcer niche The functional paralysis causing the appearance of the niche may quickly clear up under suitable therapy, with early disappearance of the deformity, or it may last for months In the third stage the development of scar tissue with callus formation greatly delays healing but does not necessarily prevent it In this stage the niche tends to persist much longer

Case histories are presented as well as a series of serial drawings of ulcers illustrating their healing to demonstrate the excellent response of ulcers to histidine and to correlate the stages of the ulcer process not only in the therapeutic successes but in the failures Histidine

49 Korbsch, R Ueber den Heilungsmechanismus des Larostidin bei Geschwüren und bei Entzündungen des Magen ein gastroskopischer Bericht, Arch f Verdauungskr 59 82, 1936

promotes healing of the ulcerating process in all stages, but in those instances in which there is a great lack of resistance of the gastric mucosa (vitamin lack), it alone may be without results. Mechanical conditions due to the formation of scar tissue also cannot be entirely remedied by injections of histidine. This form of medication is effective in a number of ways. An increased blood supply to the gastric mucosa can be readily noted through the gastroscope and also an increased tonicity of the whole wall of the stomach. The latter effect will lead to rapid disappearance of the gastric niche when it is on a paralytic basis. An increased flow of mucus is often noted. Indirectly, with the increase in appetite there is an increased intake of food, including the highly beneficial vitamins.

The author feels that repeated gastrosopic examinations give a much better idea of the progress of an ulcer coincident with histidine therapy than alleviation of symptoms or repeated roentgen examinations. He concludes that histidine is a most important *addition* to the therapy of peptic ulcer and that not only may symptoms be rapidly relieved but healing of the ulcer and of the associated gastritis may be markedly stimulated.

Gardiner⁵⁰ reports his results in a small number of cases of gastric and duodenal ulcer treated with histidine. His 12 patients were ambulatory although hospitalized, they were not on a restricted diet and received alkalis only in the beginning for postprandial pain. They received twenty-five daily injections each and were subjected to gastric analysis and roentgen studies both before and after treatment. Symptomatic relief was obtained in all the patients, and there was an invariable fall in the gastric acidity. A third of 9 patients followed for from four to six months showed a return of symptoms. It is pointed out that this form of therapy is not a cure but offers an economic saving both to the patient and to the community.

Another small series of cases is reported by Weigand.⁵¹ The usual histidine treatment was given, and most of the patients were relieved symptomatically. No marked changes in acidity were noted. Because prompt symptomatic relief is afforded, follow-up roentgen studies are important, as the organic defect frequently persists. The author's case reports emphasize this.

No evaluation of histidine therapy can be based on Behneman's⁵² report on 17 patients with peptic ulcer, all of whom became free from symptoms and one half of whom soon lost the roentgen signs of ulcera-

50 Gardiner, R. H. Histidine in the Treatment of Gastric and Duodenal Ulcer, *Lancet* **1** 1352, 1936.

51 Weigand, F. A. Histidine Treatment of Peptic Ulcer, *Pennsylvania M. J.* **39** 860, 1936.

52 Behneman, H. M. F. Late Concepts of Peptic Ulcer Etiology and a Preliminary Report of Modern Therapy, *Northwest Med.* **34** 453, 1935.

tion He treated his patients not only with daily injections of solution of levohistidine monohydrochloride but with a modified Sippy diet, gastric mucin, belladonna and sedatives However, such a combined and extensive therapeutic regimen may prove to be a greater aid to the patient than any single form of management

Sandweiss,⁵³ after a comprehensive review of the experimental data and clinical studies of others dealing with the effect of injections of histidine on the course of peptic ulcer, reports a carefully controlled series of 68 consecutive cases Seven criteria for the effect of new therapeutic measures were kept in mind throughout the course of his observations These have been lost sight of by many physicians who have enthusiastically reported on the problem, so they are enumerated here They are 1 How do the results compare with those of the diet-alkali regimen? 2 How many patients who fail to respond to diet-alkali treatment become free from symptoms with the new method? 3 Will patients tolerate a maintenance diet sooner? 4 Is the interval of freedom from symptoms prolonged, and are recurrences prevented? 5 Is gastric acidity affected? 6 What is the effect on the ulcer deformity as seen roentgenographically? 7 Are there untoward reactions?

Sandweiss' method of study was to place 23 patients who could report regularly for treatment on a course of twenty-four daily injections of histidine, the 46 who could not report regularly were started on the diet-alkali regimen Persons in one group for whom the treatment failed were then placed on the other form of therapy Consequently 53 patients were treated with diet and alkalis and 40 with histidine Those receiving injections were continued on the same diet which they had received previously Not all of them received a full course of twenty-four injections The percentage of remissions and the percentage of moderate improvement were practically the same for the two groups, approximately three fourths of all the patients were benefited In all of the 22 patients who showed remissions while receiving histidine there was a sudden disappearance of discomfort after one or two injections It was apparent that if a patient was not relieved within the first week he was not likely to be benefited later and that a full course of treatment was no more likely to prevent relapses than a short one, as 10 patients who returned with a recurrence of symptoms of ulcer within three months were among those who received twenty-four consecutive daily injections The histories are presented of 3 patients in whom symptoms were aggravated by the injections of histidine

About the same percentage of patients were relieved by injections of histidine when diet had failed as were relieved by diet when histidine failed Forty-five per cent of the patients treated with histidine were

⁵³ Sandweiss, D J Treatment of Gastroduodenal Ulcer with Histidine Monohydrochloride (Larostidin), J A M A **106** 1452 (April 25) 1936

not free from symptoms while taking a maintenance diet. Of particular interest was a recurrence of symptoms in 85 per cent of 20 patients within six months when they were treated by the injection method. A similar comparative follow-up study of 29 patients under diet-alkali management showed recurrences in only 31 per cent. No constant alteration in gastric acidity occurred. None of the 24 patients whose condition was checked by roentgen examination or by operation after histidine treatment showed disappearance of the ulcer. Forty per cent of the patients receiving injections had mild reactions. A preliminary report is included in the treatment of ulcer with daily injections of 5 cc of distilled water. In 20 patients so treated the favorable results are comparable to those obtained by injections of histidine, 60 per cent obtaining complete relief.

Sandweiss does not feel that there is sufficient experimental evidence that histidine promotes the healing of peptic ulcers or that it prevents their occurrence. From his clinical experience the use of histidine as a routine is not warranted. It should be reserved for trial in treatment of patients who do not respond to diet and alkalis, but only about 50 per cent of these may be expected to become free from symptoms.

Bulmer⁵⁴ was one of the first clinicians to report on a large series of patients with peptic ulcer treated with injections of histidine. In 1934 he published the results obtained in 52 patients. He has since treated 74 additional ambulatory patients, making a total of 126 patients, and presents not only the immediate results but, what is more important, a follow-up study of 82 of the patients, the duration of the follow-up period being from four to twenty-five months, with an average of sixteen months. The location of the ulcers was about equally divided between the stomach and the duodenum. The immediate results for the whole series were as follows: Seventy-three per cent of the patients were free from symptoms, 5 per cent were much improved and 22 per cent were unrelieved. The follow-up results for 82 of the 92 patients who were free from symptoms were as follows: Thirty-two per cent were symptom free, and 48 per cent had a relapse. No periodic injections for the prevention of relapses were tried. Bulmer concludes that histidine therapy has as good an effect on ambulatory patients as diet and alkalis but that it should be used not as an alternative but as an adjunct to the usual methods of diet and alkalis. Unfavorable effects included the occurrence of both perforation and severe hemorrhage during the treatment. (I have encountered a number of such "accidents" even in the presence of excellent symptomatic relief.) The disappearance of abnormalities roentgenographically did not necessarily mean that the ulcer had healed. Histidine treatment should be reserved for patients with simple, uncomplicated ulcers, those with "stoma-ulcer" and those for whom the usual methods have failed.

54 Bulmer, E. Histidine Treatment of Peptic Ulcer, *Lancet* 2 734, 1936

The author offers an interesting comment on supposed human deficiency of histidine as the cause of peptic ulcer. Such a known deficiency occurs only during pregnancy, and he does not recollect ever having noted a case in which peptic ulcer was coincident with pregnancy. Does peptic ulcer occur in pregnancy?

A controlled series of 41 patients with peptic ulcer treated with histidine alone is reported on from New York by Martin⁵⁵. There were 40 patients in the control group on the diet and alkali therapy for ambulatory patients. Seventy-two per cent of the group receiving the injections of histidine were relieved of symptoms, usually between the fifth and the seventh day. Those who showed an ulcer crater roentgenographically at the end of the month were less likely to be free from symptoms than those from whose roentgenograms the crater had disappeared. In 11 patients no crater was demonstrated after this short lapse of time. Thirty-nine patients were followed as long as from six to twelve months later, and 26 had had one or more relapses. Gastric acidity varied somewhat, but no constant trend toward a decrease of acidity was found. Over half the patients gained weight, this was evidently in direct proportion to the relief of symptoms and the resulting increased caloric intake. Six patients with ulcer received six injections daily of saline solution, and 3 of them were relieved of symptoms before injections of histidine could be started. In the control series of patients 78 per cent received symptomatic relief, and late relapses occurred in the usual proportion. The symptomatic and roentgenographic responses of the patients receiving histidine were not quite as good as those of the patients on the diet-alkali regimen. Martin's final conclusion is that "the therapeutic indications for histidine in the treatment of peptic ulcer are necessarily limited. The extravagant claims that have been made for this substance are unwarranted."

A one to two year follow-up study of 30 patients by Hartleb⁵⁶ showed recurrences in all but 10, some of these had followed a diet for ulcer subsequent to treatment with histidine. As in other series, many of the immediate results were good.

In a special article in the *Medical Journal of Australia* Maddox⁵⁷ gives an excellent and concise summary of the experimental and clinical work on the histidine treatment of peptic ulcer. That histidine can relieve pain is evident, and its economic advantage alone is of vast importance. However, this method has not yet had sufficient clinical trial to

55 Martin, K. A. Histidine Hydrochloride Versus Diet and Alkalis in Treatment of Peptic Ulcer, *J. A. M. A.* **106** 1468 (April 25) 1936.

56 Hartleb, H. O. Unsere Erfahrungen mit Larostidin bei ulcus ventriculi bzw. duodeni, *Med. Klin.* **32** 458, 1936.

57 Maddox, K. Histidine Treatment of Peptic Ulcers, *M. J. Australia* **1** 724 1936.

variant the discarding of other forms of treatment. At present it is of no known prophylactic value.

A series of 32 patients with peptic ulcer who received histidine treatment is reported on from Paris by Feldheim⁵⁸. The lesions were in the stomach in 6 instances and in the duodenum in 26. The patients were divided into two groups, the first, comprised of 18 patients, receiving only histidine therapy and the second, comprised of 14 patients, receiving additional medical treatment. In the first group pain ceased in almost every case on the third or fourth day of the injections, and nearly all the patients gained weight. In only 3 patients did the direct signs of hypermotility and hypersecretion seem altered. In the second group were 10 patients whose pain had not previously been relieved by the usual forms of dietary, alkali and atropine treatment. Five of these patients remained unrelieved. In only 1 instance in this group did roentgenograms show any improvement in the ulcer. The conclusion is that histidine does not influence the ulcer but that the symptom pain is relieved. Histidine treatment alone is not sufficient, but it has a definite therapeutic rôle in conjunction with other forms of medical treatment.

The numerous clinical reports of the beneficial effects of histidine therapy on peptic ulcer have aroused much curiosity. Schurch and Blangey⁵⁹ devised some experiments on young dogs to facilitate direct observations on the course of the lesions. They were able to produce typical chronic gastric and duodenal ulcers in dogs with radium. In 22 of the 27 dogs chronic ulcers developed, treatment consisted of injections of a 4 per cent solution of levohistidine monohydrochloride in an isotonic medium. Thirteen of 17 other dogs with similarly produced ulcerations served as a control series, receiving no injections. The dogs that were given histidine showed much less tendency to perforation and bleeding than the untreated animals. Also, the dogs which were treated showed a definite macroscopic and microscopic tendency toward healing of the ulcerating process as compared to the lack of healing in the control series. The authors state that no far-reaching conclusions can be drawn from this as yet unconfirmed work, particularly in relation to clinical practice.

The histidine treatment of peptic ulcer has been critically reviewed by Barry and Florey,⁶⁰ with special attention to the animal experiments on which clinical trial has been based. They have contributed some interesting operative experiments on cats and pigs to determine the effect

58 Feldheim, E. L'histidine dans la thérapeutique des ulcères gastro-duodénaux, *Presse méd* **44** 1189, 1936.

59 Schurch, O., and Blangey, R. Experimentelle Untersuchungen über die Wirkung des Larostidins beim Magengeschwür, *Deutsche Ztschr f Chir* **247** 590, 1936.

60 Barry, H. C., and Florey, H. W. Histidine Treatment of Peptic Ulcer, *Lancet* **2** 728, 1936.

of histidine on ulcers produced in these animals. The results of operation on experimental Meckel's diverticulum in cats showed chronic ulcers in the ileal loop in all 9 animals of the control series and also in a number of the 9 animals treated with histidine. Of 4 growing pigs operated on, the 1 control and all 3 which received histidine showed characteristic chronic peptic ulcers. It is emphasized that Aton's observations on dogs similarly operated on were too few, the animals were not observed over a sufficiently long period and other investigators have not obtained the same seemingly favorable results. Although most clinical reports favor the use of histidine, at least as an agent for symptomatic relief, there is still little proof that histidine has any specific action on peptic ulcer.

Gastric ulcers have been produced experimentally in rats by feeding pepsin-hydrochloric acid. Windwer and Matzner⁶¹ tested the therapeutic effect of injections of histidine monohydrochloride on rats with ulcers. In over 90 per cent of both the control group of rats and the group receiving the injections gastric lesions developed. In half of the 10 rats receiving histidine but no acid and no pepsin, gastric lesions developed, while a control group without histidine remained normal. The authors' inability to prevent gastric ulcers in rats with injections of histidine is contrary to a previous favorable report but is in keeping with similar work on other animals. It is suggested that the development of gastric lesions in rats on a normal diet plus histidine is due to the conversion of histidine into histamine, thereby adversely influencing a gastric defect. The question is raised whether or not this could occur in man.

EXPERIMENTAL GASTRIC EROSION (ULCER) PRODUCED BY A DEFICIENT DIET

Seven years ago Dam⁶² reported erosions of the gizzard in chickens with hemorrhagic disease due to dietary deficiency, later termed fowl hemophilia. Only in the last year has attention shifted from this blood dyscrasia to the gastric lesions. As these lesions have been studied up to now only by those interested primarily in the poultry industry and not by clinicians, they have continued to be designated as gizzard erosions. I have examined about two hundred and fifty gizzards containing these lesions. It is evident that they are similar to the superficial gastric ulcers (erosions) in man and that in a number of instances chronic ulcers have developed which have involved the submucosa. Gastritis is also present. As these gastric ulcers are due to a dietary deficiency and may be prevented by an adequate diet, their occurrence in the chick is of major experimental interest.

61 Windwer, C, and Matzner, M. J. Histidine in Experimental Gastric Ulcer, *Am J Digest Dis & Nutrition* **3** 547, 1936.

62 Dam, H. Cholesterinstoffwechsel in Huhnereiern und Huhnchen, *Biochem Ztschr* **215** 475, 1929.

Dam and Schonheyder⁶³ again note the presence of these ulcers in chicken gizzards and the details of the feeding experiments by which they may be produced, but Almquist and Stokstad⁶⁴ add considerable information regarding the development and prevention of the ulcerating lesions. The erosions are produced by placing newly hatched chicks on a diet lacking in all greens and all grain except rice flour and containing adequate amounts of the previously known vitamins. A hemorrhagic diathesis due to the lack of vitamin K develops in the third and fourth weeks, and if the birds die or are killed at the end of four weeks, almost 100 per cent show erosions of the gizzard to a moderate or marked degree. It was originally thought that the erosions were due purely to vitamin K deficiency. Adding alfalfa, kale, hempseed or wheat bran in adequate amounts (5 to 25 per cent of the diet) prevented the development of the lesions. Many other substances were tested for the presence of this antierosion factor, but they were all deficient.

A further series of feeding experiments revealed that extracts of certain greens were also preventive but that a far larger amount was required to prevent the formation of gastric erosions than to prevent hemorrhage. It was shown that vitamin K was in the nonsaponifiable fraction of alfalfa and that this fraction did not contain the antierosion factor. However, the saponifiable fraction did contain this factor, definitely proving that it is not identical with vitamin K, it is also readily destroyed by heat, but vitamin K is not.

It is evident that erosions (ulcers) of the gizzard in chicks caused by a deficiency in diet are due to a lack of a fat-soluble factor which is comparatively unstable and which is not identical with any of the known vitamins. When certain greens and cereals or their extracts which contain this factor are added to the diet, they prevent the development of the gastric lesions. In conjunction with this ability of an unknown dietary substance to protect the gastric mucosa from erosion, it should be stated that I have found that it is also curative. If the lesions are allowed to develop on a deficient diet and adequate amounts of alfalfa are added, restoration to a normal-appearing mucosa will take place within about three weeks.

⁶³ Dam, H., and Schonheyder, F. Occurrence and Chemical Nature of Vitamin K, *Biochem J* **30** 897, 1936.

⁶⁴ Almquist, H. J., and Stokstad, E. L. R. A Nutritional Deficiency Causing Gizzard Erosions in Chicks, *Nature, London* **137** 581, 1936, *The Gizzard Factor of the Chick, J Nutrition* **13** 339, 1937.

Obituary

JOSEPH L MILLER, M D
1867-1937

It is with a sense of deep regret and of great personal loss that the ARCHIVES OF INTERNAL MEDICINE records the death of Joseph Leggett Miller, its Editor in Chief for many years. To his devoted labors and high scientific ideals the ARCHIVES acknowledges a great debt of gratitude for whatever service it has been to medical literature.

Dr. Miller was born in Kewanee, Ill., in 1867. He graduated with a bachelor's degree from the University of Michigan and received his medical degree from Northwestern University. After graduation he entered Mercy Hospital, in Chicago, as an intern, where he served for a time with Dr. Christian Fenger. Soon after his internship he became associated with Dr. Frank Billings, and this relation continued during all the years of Dr. Billings' practice.

Dr. Miller's interest in teaching led to his appointment as instructor at Northwestern University and later at Rush Medical College, where he was promoted to an associate professorship. For the last ten years of his life he was clinical professor of medicine at the University of Chicago.

For twenty years he served on the attending staff of the Cook County Hospital, and for a long time, as president of the staff. He was senior physician at St. Luke's Hospital for the last eighteen years and sometime president of the medical board. To St. Luke's Hospital, as to all other interests, he gave unselfishly of his time and effort.

Always active in medical societies, Dr. Miller was a charter member and later president of the American Society for Clinical Investigation, and a member of the Association of American Physicians and of the Central Society for Clinical Research. He presided one year as Chairman of the Section on Medicine of the American Medical Association. He was also president of the Chicago Institute of Medicine. The results of his own clinical experience and investigation and his helpful discussion of the work of others added much to the proceedings of these societies. One of his outstanding traits was his interest in younger men and his eagerness to help and encourage them in their clinical and investigative work by his advice and counsel.

In 1918 Dr. Miller entered the United States Army as major and was later promoted to the rank of lieutenant-colonel.

Early in his career Dr. Miller was determined to spend part of his time in research. His contributions covered a wide field, including the etiology of arteriosclerosis, typhoid, foreign protein therapy, nephritis, arthritis and thyrotoxicosis.

Aside from his scientific interests, Dr Miller was an enthusiastic sportsman. No fisherman was ever more eager for the arrival of the trout season. For a week or two before going to Montana one year he was so preoccupied with rods and lines and flies that a patient



JOSEPH L MILLER, M D
1867-1937

coming out of his office remarked, "It's no use consulting Dr Miller when the trout are biting. He talked of nothing but his trip and advised me for my arthritis to go fishing."

Dr Miller's courage and honesty won him a host of friends. His example as a citizen, a patriot, a wise teacher and a scholar will long be cherished.

Book Reviews

Lane Medical Lectures Studies in Cardiovascular Regulation By G V Anrep, M D, D Sc, F R S, Professor of Physiology, the Medical Faculty of the Egyptian University, Cairo Stanford University Publications, University Series, Medical Sciences, Vol 3, No 3 Paper Price, \$1 50 Pp 118 Stanford University, Calif Stanford University Press, 1936

This volume contains the series of five lectures by Anrep given in 1936 under the sponsorship of the Lane Medical Lecture Fund at Leland Stanford University. This series is devoted to circulatory physiology and is divided into the following subjects (1) the proprioceptive mechanism of cardiovascular regulation, (2) respiratory regulation of the heart rate, (3) the dynamics of the coronary circulation, (4) the coronary blood flow and (5) the blood flow through skeletal and plain muscles.

These lectures represent a comprehensive discussion of the important experimental work in this field of physiologic research, a field in which the author's personal contributions have been outstanding.

The first two lectures are primarily a report of numerous experiments with regard to the control of the heart rate, showing the effects of changes in the pressure in the aorta and in the carotid sinus, in the oxygen and the carbon dioxide content of the blood and in the reflexes involved in the extremely complex mechanism by which the heart adapts itself, a mechanism which the author has chosen to call the proprioceptive mechanism of cardiovascular regulation.

The lectures that were most interesting to the reviewer were the two on the coronary circulation. The author cites experimental data in support of the opinion that "The contraction of the ventricle, certainly far from favoring the blood [coronary] flow, definitely impedes it. The forward rush of blood into the coronary artery which occurs during the systolic rise of the aortic blood pressure is determined by the elasticity of the coronary vessel and is not a measure of the coronary blood flow. The main blood flow through the coronary system takes place in diastole." Changes in blood pressure, the effects of cardiac rate and of changes in the oxygen and the carbon dioxide content of blood in their effect on coronary blood flow in the denervated heart are discussed. Also, the extremely difficult work on the innervated heart in the study of the influence of the vasomotor reflexes on the coronary blood flow is extremely valuable and of more than academic interest. To those whose interest is primarily in cardiovascular physiology this group of lectures should be very welcome.

On the Incidence of Anaesthetic Complications and Their Relation to Basal Narcosis By C J M Dawkins Price, 3s 6 d Pp 56 London Middlesex Hospital Press, 1936

An analysis of approximately sixteen thousand anesthetics given at several London hospitals and by the author is presented. Complications occurring during and after anesthesia are briefly considered. In two large comparable series two deaths directly attributable to the anesthetic occurred when the basal narcotic was used. The morbidity of pulmonary complications was doubled by the use of the basal narcotics, bronchitis and atelectasis being the most common. Operations involving the abdomen most frequently showed anesthetic complications. Post-operative care to prevent complications is considered.

The safest general anesthetic given was "nitrous-oxygen," supplemented by ether as needed. Other anesthetics were rarely used, because of contraindications and complications from the anesthetics themselves. Divinyl ether and cyclo-

propane have not been used enough to warrant deductions. The basal narcotics used included tribromethanol in amylene hydrate, paraldehyde and assorted barbiturates, the latter both orally and intravenously. The author prefers paraldehyde rectally as a basal narcotic, though small doses intravenously of evipal (N-methylcyclohexenylmethylmalonylurea) are used frequently.

The presentation would have been more valuable if more definite indications and contraindications regarding the use of basal narcotics had been given. In parts it is rather difficult to follow the "route" of the author's analysis. Complete statistical details and a good bibliography of both European and American literature are given. The author's conclusion that basal narcotics should not be used as a routine measure but only in certain cases, and this only with full realization of the possible complications as compared to the probable benefits, seems well justified from this analysis.

An Index of Differential Diagnosis of Main Symptoms By Various Writers. Edited by Herbert French. Fifth Edition. Price, \$16. Pp 1,145 (218 pages of index), with 742 illustrations. Baltimore. William Wood & Company, 1936.

Since this book is in its fifth edition, it is safe to say that it has filled a necessary place in the reference libraries of many physicians. If the diagnosis of disease is made easier by a thorough indexing of the symptoms, this book attains its purpose. For example, the symptom diarrhea is mentioned more than one hundred and fifty times in the index, but about ninety of these references are found on five pages. However, the rest of the references (approximately sixty) are scattered from pages 2 to 919. This is not the end of the cross-indexing of this symptom, for under "Abdomen, distention of" it is referred to as "hull diarrhea," and, finally, the symptom is last mentioned under "Zymotic diarrhea." As diarrhea is indexed, so are the other common symptoms of disease indexed. Furthermore, there is no differentiation between the terms "symptom" and "sign." They are both referred to as symptoms.

The medical student who has not finished the fifth year of medicine does not have sufficient critical judgment to use the book. The specialist will find that it falls short of his needs. The general practitioner with a limited library will no doubt find it of value.

It can be said that this book contains the most extensive cross-indexing of the signs and symptoms of disease in the English language. The difficult task of compiling such an index has been thoroughly accomplished. When and where there is need for such an index, this book may be highly recommended.

Diseases of the Coronary Arteries and Cardiac Pain Edited by Robert L. Levy, M.D., Professor of Clinical Medicine, Columbia University. Price, \$6. Pp 451, with 94 illustrations. New York. The Macmillan Company, 1936.

This monograph, on a subject of great interest to all practitioners, was prepared by a group of fourteen well known specialists, each of whom wrote one or more chapters on some phase of cardiac pain in which he is particularly interested. The result is a comprehensive volume. The manner in which the editor has assembled the material is attractive, the printing is good and the illustrations and tables that appear are clear and easily understandable.

As regards contents, all one can say is that each chapter is delightfully written and is accompanied with a good bibliography. The various phases of cardiac pain are discussed, all the way from the early history of angina pectoris and coronary occlusion through the physiology, pathology and clinical manifestations of these disorders to their most recent therapeutic attack by modern surgical methods. On the whole, the book is extremely good, it can be enthusiastically recommended to students and practitioners alike.

Medizinische Praxis Edited by R L Grote, A Fromme and K Warnekros
 Volume XIV **Elektrokardiographie für die ärztliche Praxis** By
 Erich Boden, M D, Professor of Medicine in Dusseldorf Third Edition
 Paper Price, 10 marks Pp 203, with 104 illustrations Dresden Theodor
 Steinkopff, 1936

Without doubt this is a useful booklet and deserves continued recognition by American clinicians The first edition appeared in 1932 and was reviewed in the *ARCHIVES OF INTERNAL MEDICINE* (51 640-641 [April] 1933) It was stated that this little volume was an admirable elementary exposition of electrocardiography for the practitioner, and particular praise was given the tracings and diagrams The third edition is much like the first, with reasonable amplification Again the illustrations are outstanding and commendable Again the latest edition continues to be no more than was originally intended, a first rate elementary exposition of electrocardiography for any practitioner interested in cardiac disease

Recent Advances in Endocrinology By A T Cameron Third Edition
 Price, \$5 Pp 458, with 65 illustrations Philadelphia P Blakiston's Son
 & Co, 1936

This splendid little book contains more than merely the recent advances in endocrinology It is really a small textbook The subject is treated in a scholarly way and is supplemented with an extensive bibliography, photographs and charts One is surprised to find how much important material has been compressed into a brief space The book should be equally useful to the physiologist and to the clinician

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PNEUMONIA DUE TO BACILLUS FRIEDLANDERI

A REPORT ON FORTY-ONE PATIENTS, WITH CONSIDERATION OF
SPECIFIC SERUM THERAPY

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The existence of pulmonary disease attributable to *Bacillus Friedlander* has been recognized for a number of years. Most of the previous reports have been based on isolated cases or small groups of cases, with two or three outbreaks approaching epidemic proportions. Examination of these reports reveals that they have been concerned with various features of the organism and the disease.

There have been extensive bacteriologic, cultural and immunologic studies of *Friedlander*, with more recent work on their subdivision into several morphologically identical but serologically distinct groups. These have been further concerned with the etiologic significance of the presence of *B. Friedlander* in diseased pulmonary tissue and its relative incidence in the pneumonias, in extrapulmonary diseases and in the carrier state.

Clinical study has distinguished the chronic form of the disease, which simulates pulmonary tuberculosis, from the acute fulminating form, with a uniformly high mortality rate, like that of pneumococcal lobar pneumonia. From a pathologic point of view, lobar, lobular, bronchopneumonic and mixed varieties have been noted, and a characteristic roentgenographic picture based on a corresponding pathologic concept has been described.

This study received support in part from the Metropolitan Life Insurance Company.

From the Littauer Pneumonia Research Fund, New York University, the Medical Service, the Harlem Hospital, and the Bureau of Laboratories, the Department of Health.

ETIOLOGY AND BACTERIOLOGY

The confusion in the early studies of Friedlander, Fraenkel and Weichselbaum regarding the various organisms found in pneumonic consolidations has been eliminated, and the knowledge has been adequately summarized and clarified in many of the later reports¹ It is necessary to mention here only the original difficulties in distinguishing the diplococcus of pneumonia from *B. Friedlander*, both of which were found in similarly consolidated lungs, the relegation by most observers of *B. Friedlander* to the rôle of secondary invader and, finally, the recognition that this organism serves as the sole causative agent in a definite but relatively small proportion of pulmonary infections

It is interesting, however, that even as late as 1933, Baehr, Shwartzman and Greenspan² looked on primary infection of the lung due to *B. Friedlander* as extremely rare They stated "when encountered in pneumonic and other infections of the lung it is seldom the primary cause of infection More commonly it is either a secondary invader, a contaminant, or has reached the lung from the intestinal tract, the liver, the bile passages, or the urinary tract, by the blood stream or by direct extension"

Considerable bacteriologic and immunologic study has defined the position of *B. Friedlander* in relation to the colon-typhoid-enteric group of gram-negative bacilli *B. Friedlander* may be described as gram-negative encapsulated bacilli varying from short forms, resembling diplococci, to thin rods and thick forms The organisms may occur singly, as diplobacilli, or in chains and sheets, and they grow readily on culture at room temperature, yielding large viscid colonies on plates and a slimy pellicle in broth

The serologic classification of Julianelle³ has distinguished the different strains involved in human and in animal infections A classification of this type is vital to rational attempts at serum therapy Julianelle recognized A, B and C types and an X group of unclassified strains

1 (a) Sisson, W. R., and Thompson, C. B. *Friedlander Bacillus Pneumonia, with Report of Cases*, *Am J M Sc* **150** 713 (Nov.) 1915 (b) Belk, W. P. *Pulmonary Infections by Friedlander's Bacillus*, *J Infect Dis* **38** 115 (Feb.) 1926 (c) Sweany, H. C., Stadnichenko, A., and Henrichsen, K. J. *Multiple Pulmonary Abscesses Simulating Tuberculosis Caused by Friedlander's Bacillus*, *Arch Int Med* **47** 565 (April) 1931 (d) Fremmel, F., Henrichsen, K. J., and Sweany, H. C. *Pulmonary Infections by Friedlander's Bacillus*, *Ann Int Med* **5** 886 (Jan.) 1932 (e) Olcott, C. T. *Pneumonia Due to Friedlander's Bacillus*, *Arch Path* **16** 471 (Oct.) 1933

2 Baehr, G., Shwartzman, G., and Greenspan, E. B. *The Rôle of Bacillus Friedlander in Infection*, *Tr A Am Physicians* **48** 353, 1933

3 Julianelle, L. A. *The Distribution of Friedlander's Bacilli of Different Types*, *J Exper Med* **52** 439 (Oct.) 1930

This nomenclature was used by us in the identification of the organisms in our cases. Classifications on the basis of fermentation reactions were unsatisfactory and did not parallel serologic groupings.

Avery, Heidelberger and Goebel⁴ demonstrated chemical as well as immunologic relationships between *Pneumococcus* type II and a strain of *B. Friedlander*, later identified as *B. Friedlander* of type B, and Goebel⁵ called attention to the isomeric relationship between the aldonic acids present in the specific soluble carbohydrates in the capsules of *B. Friedlander* A and that of *Pneumococcus* type II, although he noted no immunologic resemblance.

INCIDENCE

The reported incidence of *B. Friedlander* as the causative agent in pneumonia varies. In a series of 2,000 cases of pneumonia, Cecil, Baldwin and Larsen⁶ found a 0.4 per cent incidence of pure infections, whereas Gay⁷ said he believed the incidence to be as high as from 8 to 10 per cent in croupous and still higher in bronchopneumonic and mixed infections. Bhatnagar and Singh⁸ recently reported 13 cases of pneumonia due to *B. Friedlander* in a series of 100 cases of pneumonia in India. In a series of 3,768 cases of pneumonia among adults studied bacteriologically at the Harlem Hospital from 1929 to 1936, 41 instances of pneumonia due to *B. Friedlander* were noted, comprising 1.1 per cent of the total number of cases.

In the upper portion of the so-called normal respiratory tract Bloomfield⁹ found the bacillus in 5.8 per cent of 85 unselected cases, with the most frequent localization in the tonsils. In the carrier state Gay⁷ mentioned it as existing in up to 25 per cent of normal human beings. Among 855 cases in which secretions of the respiratory tract were

4 Avery, O. T., Heidelberger, M., and Goebel, W. F. The Soluble Specific Substance of Friedlander's Bacillus. II. Chemical and Immunological Relationships of *Pneumococcus* Type II and of a Strain of Friedlander's Bacillus, *J. Exper. Med.* **42**: 709 (Nov.) 1925.

5 Goebel, W. F. The Soluble Specific Substance of Friedlander's Bacillus. IV. On the Nature of the Hydrolytic Products of the Specific Carbohydrate from Type A Friedlander Bacillus, *J. Biol. Chem.* **74**: 619 (Sept.) 1927.

6 Cecil, R. L., Baldwin, H. S., and Larsen, N. P. Lobar Pneumonia. A Clinical and Bacteriologic Study of Two Thousand Typed Cases, *Arch. Int. Med.* **40**: 253 (Sept.) 1927.

7 Gay, F. P., and others. Agents of Disease and Host Resistance, Springfield, Ill., Charles C. Thomas, Publisher, 1935.

8 Bhatnagar, S. S., and Singh, K. Bacteriological Studies in Acute Lobar Pneumonia Due to *Pneumococcus* and *B. Pneumoniae* Friedlander, *Indian J. M. Research* **23**: 337 (Oct.) 1935.

9 Bloomfield, A. L. The Mechanism of the Bacillus Carrier, with Special Reference to the Friedlander Bacillus, *Am. Rev. Tuberc.* **4**: 847 (Jan.) 1921.

studied bacteriologically in the medical service at the Harlem Hospital (the patients were suffering chiefly from miscellaneous infections of the respiratory tract), *B. Friedlander* was found in 19 (22 per cent). In 11 of these cases *B. Friedlander* of type A was present. Pneumococci were found in 593 cases (69 per cent).

The organism has also been found in chronic pulmonary abscess, influenza, empyema and miscellaneous infections of the bronchial tree and larynx.

The pathogenicity of *B. Friedlander* in man is not limited to the respiratory tract. The organism has been found to involve the gastrointestinal and genito-urinary tracts, and it frequently invades the blood stream as well.

Although most of the cases of pneumonia reported as due to *B. Friedlander* were isolated instances or appeared in small groups, several outbreaks approaching epidemic proportions have been reported, the most prominent being the one cited by Zander¹⁰ in 1919. He described several hundred cases of pneumonia due to *B. Friedlander* occurring chiefly in patients below middle age. There was a mean duration of illness of nine and one-half days, and the mortality was approximately 29 per cent. Zander noted the occurrence of relapses and the tendency toward transition from the active to the carrier state. Khewe¹¹ reported an epidemic of infections of the upper portion of the respiratory tract and of the lungs due to *B. Friedlander* in 11 children who were exposed to a patient with pneumonia known to be due to *B. Friedlander*. Jampolis, Howell, Calvin and Leventhal¹² reported an outbreak of gastroenteritis attributable to *B. Friedlander*, several cases of which were complicated by invasion of the blood stream and pulmonary involvement. In the present study of 41 cases, a fairly even distribution over a seven year period was noted, except for November 1935. During that month there were 5 cases, all of which began within the span of a few days. Of these 5 cases, 4 were caused by *B. Friedlander* A, and the fifth, by an unclassified *B. Friedlander* (not an A). The appearance of 5 cases in one month, as contrasted with 41 cases distributed over a period of seven years, appears to be of epidemiologic significance.

10 Zander. Ausgedehnte Endemie von Lungenentzündungen durch Infektion mit Friedlanderschen Pneumobazillen unter Zivilarbeiten, *Deutsche med Wchnschr* **45** 1180, 1919.

11 Khewe, H. Epidemiologische und biologische Studien über den *B. pneumoniae* Friedlander und verwandte Arten, *Zentralbl f Bakt (Abt 1)* **116** 92, 1930.

12 Jampolis, M., Howell, K. M., Calvin, J. K., and Leventhal, M. L. *Bacillus Mucosus* Infection of the New-Born, *Am J Dis Child* **43** 70 (Jan.) 1932.

CLINICAL AND PATHOLOGIC STUDIES

Most observers in the past have described in detail the gross and microscopic observations in pulmonary consolidations caused by *B. Friedlanderi*. Their descriptions are fairly consistent as regards the massive consolidation, the viscid exudate and the tissue necrosis which results in gross and microscopic abscesses, with and without cavitation. They have also recorded the marked cytolysis, the hemorrhage, the mononuclear and polymorphonuclear alveolar exudates and the widespread overgrowth of easily recognizable bacilli, with extensive phagocytosis. The interpretation of these features, however, varied considerably when attempts were made to classify the consolidation as lobar, lobular, confluent lobular or bronchopneumonic. Most observers hesitated to call the massive consolidation "lobar," preferring to designate it as lobular or confluent lobular.

A chronic remissive form, resembling and frequently mistaken for pulmonary tuberculosis, has been described. This variety followed the onset of acute pneumonia in the case described separately by Berglund¹³ and Westermarck¹⁴ and persisted for nine years in the case reported by Brulé, Huguenin and Dreyfus¹⁵. The chronic form is characterized by remissions and exacerbations, with pulmonary cavitation, fibrosis and bronchiectasis. Sweany, Stadnichenko and Henrichsen¹⁶ discussed the chronic aspect of the disease and the pathogenesis of infection of the lung due to *B. Friedlanderi* as beginning with bacterial spread, mononuclear phagocytosis and hemorrhage, followed by polymorphonuclear infiltration, vascular engorgement, thrombosis and, finally, resolution with necrosis.

Reconstruction of the disease process was attempted by Kornblum and Collins¹⁶ by means of repeated roentgenographic studies. They visualized four consecutive stages: (1) incipient bronchopneumonia, followed by (2) secondary pseudolobar confluence, which soon breaks down and results in (3) the formation of multiple thin-walled abscess cavities and goes on to (4) a stage of fibrosis and healing. They con-

13 Berglund, N. Fall von Friedlanderpneumonie unter dem Bilde einer Lungentuberkulose. Terminale Affektion der Harnwege, Beitr z Klin d Tuberk **62** 745, 1925-1926.

14 Westermarck, N. Ein Tuberkulose vortauschender Fall von Friedlander's Pneumonia mit lange sich hinziehendem Verlauf, Acta radiol **7** 626, 1926.

15 Brulé, M., Huguenin, R., and Gilbert-Dreyfus. Pneumopathie chronique à bacilles de Friedlander, Bull et mem Soc méd d hôp de Paris **51** 1370 (Oct) 1927.

16 Kornblum, K. The Roentgen-Ray Diagnosis of Pulmonary Infections with the Friedlander Bacillus, Am J Roentgenol **19** 513 (June) 1928. Collins, J. H., Jr., and Kornblum, K. Chronic Pulmonary Infection Due to Friedlander's Bacillus. A Clinical and Roentgenologic Study, Arch Int Med **43** 351 (March) 1929.

TABLE 1—Data for Patients Not Receiving Serum

Case No	Initials	Color	Time of Illness	Sex	Age	Onset	Lobes involved	Causative Organism*	Course	Duration of Illness, Days	Results of Blood Culture
1	N T	N	Oct 1932	M	50	Infection of upper respiratory tract, chilliness	RUL RML RLL	BFA	Leukopenia, death	9	+
2	R M	W	Jan 1933	M	73	?	LLL	BFB	Leukopenia, death	2(?)	+
3	D D	N	Jan 1933	M	31	Typical pneumonic infection	RUL	BFA	Leukopenia, respiratory distress, death Necropsy coarse granular red and gray hepatization of RUL and RML	2	+
4	H I	W	March 1933	M	62	Typical pneumonic infection	LUL LLL	BFA	Pulmonary edema, death	7	+
5	R B	N	April 1933	M	42	Infection of upper respiratory tract, typical pneumonia	RUL RML RLL	BFA	Pulmonary edema, death	3	—
6	R M	N	June 1933	M	47	Typical pneumonia, headache	RUL	BF	Leukopenia, peripheral vascular collapse, death	9	+
7	H K	W	June 1933	M	51	Alcoholic indulgence, submergence, typical pneumonia, no chill	RLL LLL	BFB	Leukopenia, pulmonary edema, hyperpyrexia death	3	+
8	J D	W	Sept 1935	M	43	Chronic cough, typical pneumonia	RLL	BF (not A)	Death	3	+
9	M B	N	Aug 1935	M	51	Typical pneumonia, no chill	RUL RML RLL	BFA	Peripheral vascular collapse, death Necropsy red granular hepatization of RUL, RML and RLL	6	+
10	T J	W	Nov 1935	M	60	Typical pneumonia	RUL LLL	BF (not A)	Peripheral vascular collapse, death	3	+
11	R J	N	Nov 1935	M	29	Infection of upper respiratory tract, typical pneumonia	LUL LLL	BFA	Leukopenia, delirium, death	4	+
12	P J	N	Nov 1935	M	29	Typical pneumonia	RUL RML RLL	BFA	Leukopenia death	2	+
13	B G	N	Nov 1935	M	42	Alcoholic indulgence, cough, emesis	LUL	BFA	Leukopenia, distention, delirium, death	5	+
14	E M	N	Feb 1931	M	36	? Cough, pain	RUL	BF	Herpes, cavitation, recovery	?	—
15	L P	N	Feb 1936	F	68	Typical pneumonia	LUL	BFA	Pulmonary edema death	4	—
16	T S	W	Jan 1934	M	65	Alcoholic indulgence chronic cough typical pneumonia	RLL LLL	BFA PV	Delirium death	10	+

17	E M	N	Jan 1934	F	37	Typical pneumonia	RLL	BFA	Delirium, hyperpyrexia, death	13	+
18	W S	N	Jan 1934	M	70	Typical pneumonia	RLL	BF	Pulmonary edema, death Necropsy gray hepatization of RLL	11	+
19	M B	N	Sept 1934	F	32	Typical pneumonia, emesis	LUL	BF (not A)	Incontinence, delirium, hyperpyrexia, death	5	+
20	O T	N	Sept 1934	M	43	Typical pneumonia, abdominal pain, diarrhea	RUL	BFA	Peripheral vascular collapse, death Necropsy, gray yellow consolidation of RUL, with hemorrhage	6	-
21	L M	N	Nov 1934	M	38	Infection of upper respiratory tract, thro racic pain, emesis	RUL	BFA	Leukopenia, peripheral vascular collapse, death	5	-
22	W H	N	Oct 1934	M	42	Typical pneumonia	RML RLL	BFA	Death Necropsy gray hepatization of RML and RLL, with abscess	6	+
23	W J	N	Nov 1934	M	58	Typical pneumonia, diarrhea, emesis	RLL	BFA	Respiratory distress, death	3	-
24	J A	W	Jan 1935	M	47	Typical pneumonia, hemoptysis, erythema	RUL	BFA	Peripheral vascular collapse, death	5	+
25	M N	N	June 1929	F	58	Exposure, typical pneumonia, no pain	RUL LLL	BF	Pulmonary edema, death	6	+
26	M B	N	Jan 1930	M	49	Thoracic trauma, typical pneumonia, emesis, hemoptysis	RLL	BF	Leukopenia, death	3	+
27	A W	N	May 1931	F	31	Typical pneumonia	RLL LLL	BFD	Delirium, death Necropsy, grayish pink consolidation of LLL, with abscess and bronchial necrosis, similar patch in RLL	12	+
28	I B	N	May 1931	M	51	Alcoholic indulgence, typical pneumonia, no chill	RLL	BF	Diarrhea, death Necropsy gray hepatization of RLL and RML and half of RUL, red hepatization of RML	5	+
29	J T	N	Jan 1932	M	59	Typical pneumonia, no chill, emesis	LLL	BFA	Delirium, death	3	-
30	R L	N	Sept 1931	M	77	Typical pneumonia, no chill	LLL	BF	Leukopenia, pulmonary edema, death Necropsy gray hepatization of LLL	21	+
31	J H	N	March 1932	M	48	Coma	RUL RML RLL	BF (not A)	Respiratory distress, peripheral vascular collapse, death	22	-
32	O W	N	Sept 1935	M	57	Typical pneumonia, no chill	RUL	BFA	Recovery	10	-
33	J J	N	July 1935	M	41	Typical pneumonia, delirium	RUL RML RLL	BFO	Diarrhea, melena, recovery	11	+

* BF Indicates B Friedlander, the type (A, B, C, or D) being designated when known PV Indicates Pneumococcus type V

sidered, as did Hart,¹⁷ that the roentgenographic picture of multiple thin-walled cavities was characteristic of the disease. Collins made a follow-up study in several cases for from two to seven years, and in his recent survey¹⁸ he reemphasized the resemblance to chronic pulmonary tuberculosis.

French writers¹⁹ have classified the various types of involvement as follows: (1) the *hyperacute* or *superacute* type, characterized by overwhelming toxicity, massive consolidation and an almost invariably fatal termination, (2) the *acute* type, characterized by hepatization, with abscess formation, and occasionally by recovery, and (3) the *subacute* or *subacute suppurative pneumonic* type, in which the patient survives the acute stage and experiences an extended period of remission and exacerbation, ultimately showing clinical and roentgenographic evidence of cavitation.

Pathologically, they classified the lesions into the lobar group, the bronchopneumonic group and the pseudopneumonic group, the last being considered typical of infection due to *B. Friedländeri*. They expressed doubt that *B. Friedländeri* alone could give rise to a purely lobar distribution without the presence of a primary or of an associated pneumococcal invader.

The strikingly fulminating clinical course of acute pneumonia due to *B. Friedländeri* as well as the uniformly high mortality has been well recognized by most observers, and, except for minor individual variations, their findings agree in essence with ours, which will now be described in detail.

REPORT OF CASES

Forty-one patients (tables 1 and 2) with pneumonia due to *B. Friedländeri* were studied at the Harlem Hospital during the seven year period from June 1929 to June 1936. The diagnosis of pneumonia in each case was made by clinical and roentgenographic study, and *B. Friedländeri* was recovered either from the blood or from the material obtained by pulmonary suction or from both, as well as from the sputum.

17 Hart, A. L. The Postpneumonic Lung. A Critical Review, *Am J Roentgenol* 26:371 (Sept.) 1931.

18 Collins, L. H., Jr. Chronic Pulmonary Infection Due to the *Friedländer Bacillus*. Further Observations, *Arch Int Med* 58:235 (Aug.) 1936.

19 Macaigne, M. *Maladies infectieuses*, in Roger, G. E. H., Widal, F., and Teissier, P. J. *Nouveau traité de médecine et de thérapeutique*, Paris, Masson & Cie, 1920. Letulle, M., and Bezançon, F. La pneumonie dissequante nécrotique, *Ann de med* 12:1 (July) 1922. Lemierre, A., and Levesque, J. Les pneumopathies à pneumobacilles de *Friedländer*, *Arch med-chir de l'app respir* 2:97 (April) 1927. Stoichita, N. N., and Jonnesco, D. Abscess du poulmon et septicémie à pneumobacilles de *Friedländer*, *ibid* 8:534, 1933.

TABLE 2—Data for Patients Recovering Serum

Case No	Initials	Color	Time of Illness	Sex	Age	Onset	Lobes Involved	Causative Organism	Course	Duration of Illness, Days	Result of Blood Culture
1	L B	N	April 1931	M	28	Typical pneumonia, emesis, arthritis	RLL	BF	Herpes, epistaxis, delirium, recovery	6	+
2	L O	W	May 1932	M	45	Typical pneumonia, emesis	RUL	BFA	Leukopenia, meningeal involvement, hyperpyrexia, death	10	+
3	J W	N	Nov 1932	M	36	Typical pneumonia, no chill	LLL	BFA	Recovery	8	—
4	J W (case 3)	N	Jan 1935	M	38	Typical pneumonia	RUL	BFA	Distention, delirium, peripheral vascular collapse, death Necropsy: gray granular consolidation of RUL adhesions of left lung	4	—
5	E S	W	Nov 1935	M	53	Typical pneumonia	RUL	BFA	Erythema, leukopenia, peripheral vascular collapse, death	4	—
6	E T	W	Oct 1935	M	52	Thoracic trauma, infection of upper respiratory tract, typical pneumonia	RUL	BFA	Leukopenia, delirium, recovery	12	—
7	J W	N	Aug 1932	M	26	Typical pneumonia	RLL	BFA	Recovery, serum sickness	7	—
8A	A M	N	May 1936	M	43	Typical pneumonia	RLL	BF (not 1)	Delirium, death Necropsy: gray hepatization of RLL	1	+

In view of the reported high incidence of *B. Friedlander* in the carrier state, 4 patients, 3 of whom died, who presented positive findings only in the sputum were not included in this series

The organisms were identified and typed and are shown classified into serologic groups in table 3. Swelling of the capsule took place with the homologous antiserum as it occurs with the pneumococcus under similar conditions. Pulmonary suction was performed in all cases as soon as the presence of consolidation was established. The positive results of growth of material obtained by pulmonary suction during life in the presence of positive results of blood culture is, of course, of doubtful significance, since some blood may be aspirated through the needle. However, positive results of pulmonary suction confirming the sputum findings were obtained for 19 patients at the time the blood cultures were sterile. In one instance a typical viscid exudate was aspirated, while in another direct smear of the material aspirated revealed the presence of numerous *Friedlander* bacilli.

TABLE 3—*Distribution of Cases According to Type of Infecting Organism, Bacteremia and Mortality*^{*}

Type of <i>B. Friedlander</i>	Total No. of Cases	Deaths		Recoveries	
		Total	Bacteremia	Total	Bacteremia
A	24	20	(12)	4	(0)
B	2	2	(2)	0	0
C	1	0	0	1	(1)
Untyped (not A)*	6	6	(5)	0	0
Untyped	8	6	(6)	2	(1)
	41	34	(25)	7	(2)

* Tested only for type A

The distribution of the 41 cases over the seven year period is shown in figure 1. In the entire group there were 36 (or 88 per cent) men, 10 of whom were white and 26, Negroes. All 5 women were Negroes. The distribution by age is shown in figure 2.

Such predisposing factors as alcoholism, trauma, submergence and chronic nontuberculous pulmonary disease were present only occasionally. Twenty-one, or approximately half, of our patients contracted the disease with the suddenness characteristic of pneumococcal lobar pneumonia and presented the typical chill, pleural pain and cough productive of blood-stained sputum. Profound and rapidly progressive prostration was characteristic. The physical signs of consolidation were commonly classic, but occasionally a patient presented practically no physical signs, in spite of the most extensive involvement revealed by the roentgenogram or by the postmortem examination. Coarse moist râles were frequently noted.

In two thirds of the patients the sputum did not differ grossly from that seen in pneumococcic lobar pneumonia, being either blood-tinged or rusty. The remaining third, however, showed sputum which has been frequently described as typical of pneumonia due to *B. Friedlander*, being thick, gelatinous and diffusely bloody. It was expectorated copiously but with difficulty, adhering to the lips of the patient and to the sputum cup. Some of the patients had free hemoptysis, others occasionally expectorated a thin sputum resembling currant jelly.

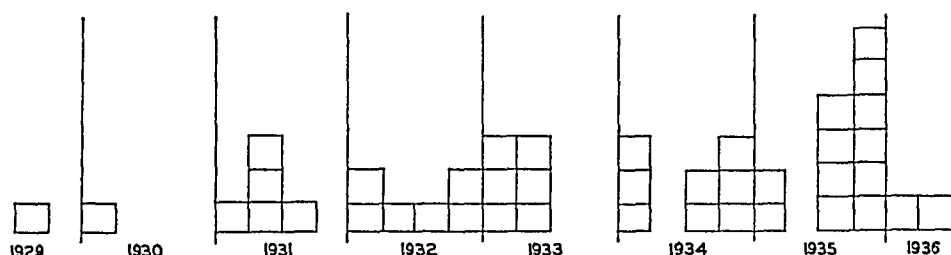


Fig 1—Distribution of pneumonia due to *Friedlander's* bacillus. Each square represents 1 case.

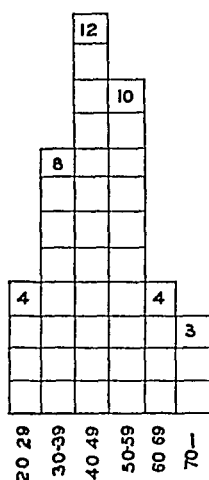


Fig 2—Distribution of pneumonia due to *Friedlander's* bacillus according to the ages of the patients.

Microscopically, the sputum was usually found to be teeming with gram-negative encapsulated bacilli, varying in thickness and in length and lying singly, in short chains or as diplobacilli.

The distribution of the consolidation was usually purely lobar, although not infrequently the process extended beyond the interlobar fissure and involved the adjacent pulmonary tissue. Isolated patches were occasionally noted on the same or on the opposite side. In a few patients diffuse and irregular involvement was noted, as in one patient in whom submergence was a predisposing factor. The distribution by lobes is given in figure 3. In 32 of the 41 patients there was complete

or partial involvement of the right lung, as contrasted with involvement of the left side in 14 patients. One of the 6 patients with complete consolidation of the right lung recovered, not any of the 5 patients with bilateral involvement recovered.

The course of the illness was not marked by any unusual preponderance of extrapulmonary manifestations. Ten patients had associated gastro-enteritis, with vomiting and diarrhea, and in 1 instance melena was present. Two patients presented extensive erythemas, 1 of which was scarlatiniform. Three patients manifested delirium early,

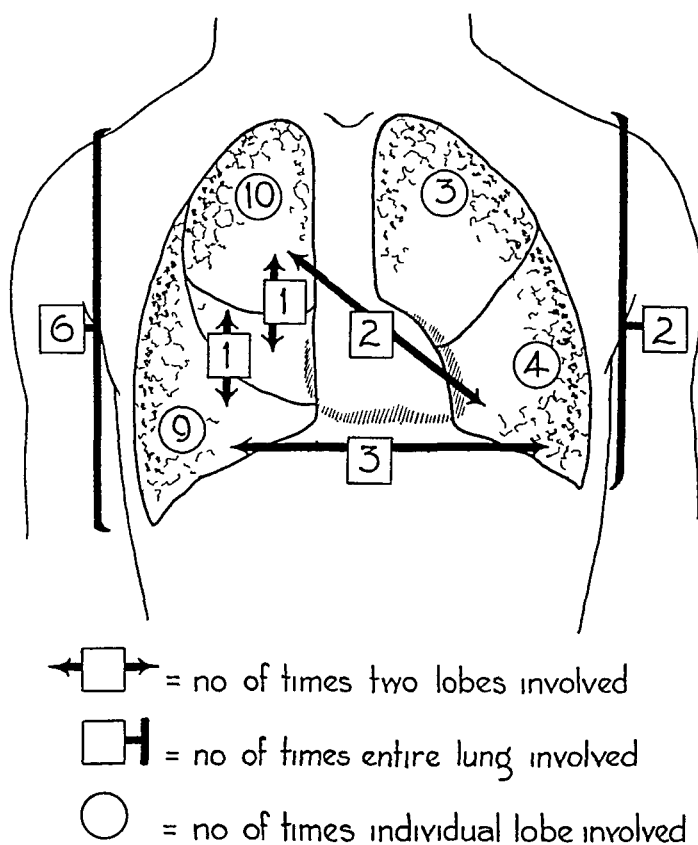


Fig 3—Distribution of the pneumonic consolidation in 41 patients

but headache was prominent in only 1 patient. Six patients showed clinical, bacteriologic or pathologic evidence of meningeal involvement, and in only 1 of these did it occur in the absence of positive results of blood culture. No meningeal involvement was observed in the patients treated with serum or in those who recovered without serum treatment. Herpes occurred twice and epistaxis once, a nonsuppurative polyarthritis was noted in 1 patient.

Characteristic of the clinical course was the rapid dissolution. Fremmel, Henrichsen and Sweany¹⁴ reported on a patient who showed

typical involvement, with death occurring twenty-six hours after the onset. The shortest duration observed by us was thirty hours, and the average duration from onset to death was five and one-half days, with three fourths of the patients living six days or less. This may be compared with the findings for patients with lobar pneumonia due to *Pneumococcus* type II observed by us during a similar period for whom the average duration from onset to death was nine days.

The mode of termination varied. Nine patients died in peripheral vascular collapse, 7 of pulmonary edema and 3 of extreme respiratory

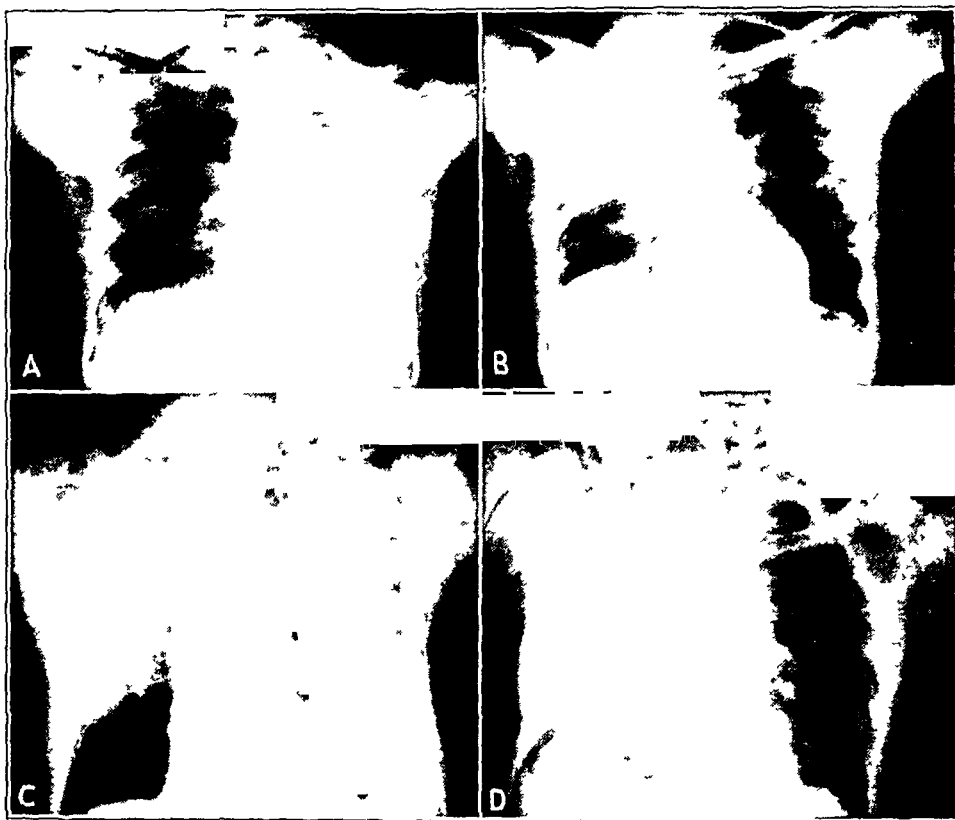


Fig 4—A, J W (table 2, case 3), a man aged 36, had a typical pneumonic invasion which lasted for eight days. The infection, due to *B. Friedlander*, A, involved the lower lobe of the left lung. Serum treatment was given. B, the same patient when 39 years old had a typical pneumonic invasion, with distention, delirium and peripheral vascular collapse. *B. Friedlander*, A was the cause of the infection. The upper lobe of the right lung showed gray granular consolidation, and there was pleural adhesion in the left lung. Death occurred on the fourth day. C, E S (table 2, case 5), a man aged 53, had a typical pneumonic invasion of the upper lobe of the right lung, with erythematous eruption, leukopenia and peripheral vascular collapse. Death occurred on the fourth day in spite of serum therapy. *B. Friedlander*, A was the cause of the involvement. D, R M (table 1, case 6), a man aged 47, showed typical pneumonic invasion of the upper lobe of the right lung, with headache, leukopenia and peripheral vascular collapse. Death occurred on the ninth day. Bacteremia was present, *Friedlander's bacillus* being recovered. Serum treatment was not given.

distress without pulmonary edema. Ten were in delirium, 2 showed uncontrollable distention and 1 was incontinent terminally. Four showed terminal hyperpyrexia, and relatively trivial procedures, such as venipuncture for blood culture, preceded death in a few instances.

The blood count showed conditions which varied between polymorphonuclear leukocytosis and the frequently described leukopenia. The latter was found in 14, or approximately one third, of our patients and was occasionally marked by an extreme preponderance of immature forms. The urine showed the usual changes found in febrile states. The curves for temperature and pulse and respiratory rates did not differ



Fig 5—*A*, *A M* (table 2, case 8), a Negro aged 43, had a typical pneumonic infection with Friedlander's bacillus (not *A*) of the lower lobe of the right lung. The patient was delirious and died during the first day of illness. Necropsy revealed gray hepatization. *B*, *M B* (table 1, case 9), a man aged 51, had a typical pneumonic invasion without chill but with peripheral vascular collapse. Death occurred on the sixth day. Bacteremia was present, *B* Friedlander's *A* being recovered. All three lobes of the right lung were involved. *C*, *C T* (table 1, case 20), a man aged 43, had a typical pneumonic invasion, with abdominal pain, diarrhea and peripheral vascular collapse. Death occurred on the sixth day. *B* Friedlander's *A* was the cause of the infection of the upper lobe of the right lung.

significantly from those of pneumococcic lobar pneumonia. The temperature curves varied from sustained elevations to spiking, low or markedly irregular varieties. No single type seemed to predominate.

Roentgenographic studies of the chest showed the predominant finding to be a massive, dense, usually homogeneous shadow which was frequently suggestive of fluid. We were able to study 6 patients within forty-eight hours of onset, and in only 1 of them did we see the mottled roentgenographic appearance which Kornblum and others described as characteristic and from which they drew their conception as to the bronchopneumonic nature of the disease.

Thirty-four, or 83 per cent, of the entire group of patients died. Twenty-seven, or 66 per cent, showed positive results of blood culture either during the course of the illness or terminally, 25, or 93 per cent, of these patients died. One patient (T S) showed *B. Friedlander*, *A* and *Pneumococcus* type V repeatedly on pulmonary suction and blood culture and must be considered as showing a true mixed infection.

The available data obtained from a study of the agglutinins of the blood did not permit any definite conclusions to be drawn.



Fig 6—C W (table 1, case 32), a man aged 57, had a typical pneumonic invasion without a chill. *B. Friedlander*, *A* was the causative agent. The patient was febrile for eleven days. Recovery followed. *A*, the involvement of the upper lobe of the right lung, with pneumothorax induced by pulmonary suction, *B*, the residual cavitation.

In the 10 patients who came to necropsy (performed by Dr S Weintraub, pathologist) the predominant lesion was a massive lobar consolidation, the gray-yellow granular lung containing a viscid gelatinous exudate. Red hepatization was seen on 3 occasions, and abscess formation in the consolidated areas was noted twice. The abscess consisted of soft liquefied areas without pyogenic or cell-reactive membranes. Similar aputrid necroses were noted by us as well as by others in pneumococcal lobar pneumonia, particularly in pneumonia caused by *Pneumococcus* type III. Kessel²⁰ described similar obser-

²⁰ Kessel, L. The Clinical Aspect of Aputrid Pulmonary Necrosis, *Arch Int Med* 45:401 (March) 1930.

vations in 2 patients with lobar pneumonia due to *Pneumococcus* type II. Subpleural and intrapulmonary bleeding and fibrinopurulent pleuritis were also observed. The patients who recovered and who were followed up with roentgenographic examinations showed thickened pleurae or fibrosis, and in 1 patient excavation of the upper lobe of the right lung was noted. Microscopic studies of pulmonary tissue were

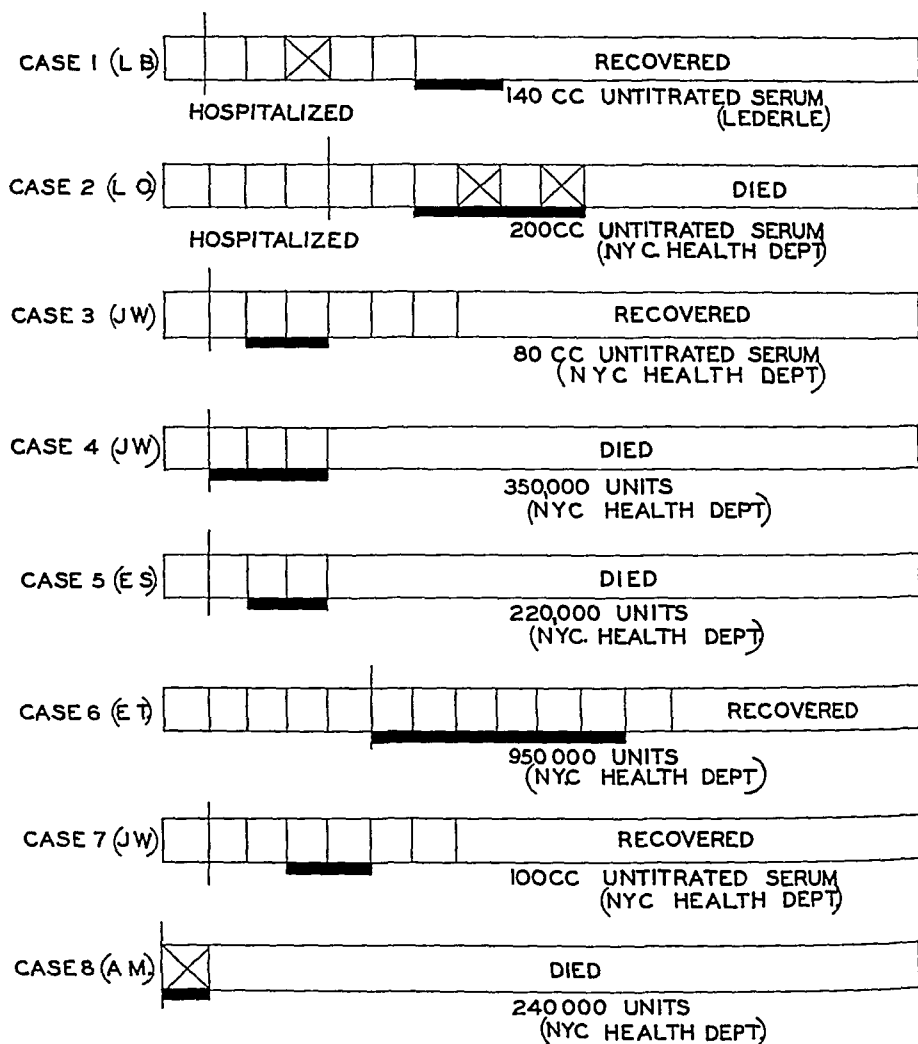


Fig 7—Serum treatment of patients with pneumonia due to Friedlander's bacillus (*Klebsiella pneumoniae*). Each square represents one day of illness. Crosses indicate positive results of blood culture.

in accord with those reported by other observers. The predominance of mononuclear alveolar exudates was noted, but polymorphonuclear infiltration was observed in 1 patient and granular edema in another.

Serum Therapy—Specific serum therapy with B. Friedlander's antiserum was attempted by us for 8 patients (table 2 and figure 4).

L B (table 2, case 1) was infected with an untyped B Friedlander₁ and, in addition, received B Friedlander₁ A antiserum after clinical recovery had already begun. Hence, this will not be considered as recovery due to serum treatment. L O (case 2) was given serum on the seventh day of illness. Death occurred on the eleventh day. J W (case 3) had pneumonia due to B Friedlander₁ A which was limited to the lower lobe of the left lung. Serum was given on the third day, and recovery followed. The patient returned to the hospital twenty-six months later (case 4) with pneumonia due to B Friedlander₁ A in the upper lobe of the right lung and died in spite of vigorous serum therapy instituted on the second day. At necropsy there were no parenchymal residua in the lung which had been involved twenty-six months previously. E S (case 5) entered with complete consolidation of the right lung, received serum on the third day and died in pulmonary edema. E T (case 6) had consolidation of the upper lobe of the right lung associated with leukopenia and complicated by delirium. He received serum on the sixth day and recovered. J W (case 7) received serum on the fourth day, recovery was complicated by serum sickness. A M (case 8) received B Friedlander₁ A serum on the first day and died. He was found to be infected with an unclassified strain of B Friedlander₁ which was not of type A. His death will be considered as occurring without serum treatment as the serum given was not specifically related to the infecting organism.

Omitting L B and A M (cases 1 and 8) from the group of patients treated, there were 6 patients treated with specific serum and 35 not so treated. Thirty (or 89 per cent) of the 35 patients who were not given serum died. Of these, 18 had infections due to B Friedlander₁ A, and 17 (or 94 per cent) died. In 10 of these there was bacteremia, and in the 1 patient with pneumonia due to B Friedlander₁ type A who recovered without the use of serum the blood culture was persistently sterile. Three (or 50 per cent) of the 6 with infections due to B Friedlander₁ A who received specific serum therapy succumbed. The blood of the 3 who recovered was not invaded.

Although pneumonia due to B Friedlander₁ is not commonly encountered, its fulminating course and high mortality present therapeutic difficulties and opportunities. While the patients treated by us with specific serum are far too few to permit the drawing of definite conclusions as to the value of serotherapy, the absence of other adequate therapeutic agents and the success which has attended serum therapy in related conditions warrant further attempts in this direction. Because of the fulminating character of the disease and the recognition that serum therapy, if it is to be at all effective, must be administered as early as possible, it is suggested that for every patient with lobar pneumonia who appears toxic out of proportion to the pulmonary

involvement and whose sputum suggests grossly the appearance described, a microscopic examination of sputum by direct smear be made at once. If the easily recognizable *B. Friedlander*i is found and can be typed, specific serum therapy should be instituted.

SUMMARY

A report on 41 patients with acute pneumonia due to *B. Friedlander*i is presented in an attempt to portray the disease as a clinical and pathologic entity. The findings for these patients showed a marked similarity to those for patients with pneumococcic lobar pneumonia.

The mortality rate for the entire group of 41 patients was 83 per cent. The highest mortality rate (94 per cent) occurred in patients infected with *B. Friedlander*i A who were not given serum.

Serum therapy was attempted for 8 of the patients, but in only 6 of them was the serum specifically related to the infecting organism. The mortality rate for these 6 patients who were infected with *B. Friedlander*i A and who received serum was 50 per cent, as contrasted with a mortality rate of 94 per cent for the 18 patients infected with the same organism and not treated with serum.

NOTE—Since the preparation of our report Solomon²¹ has published reports of 5 patients from Bellevue Hospital. Only 1 patient was treated as early as the third day. The 4 others were treated on the fifth day or later. The amount of serum given was inadequate. All his patients who received serum died.

21 Solomon, Saul. Primary Friedlander Pneumonia, *J. A. M. A.* 108:937 (March 20) 1937.

HYPERINSULINISM

FINAL REPORT OF CASE INCLUDING NECROPSY OBSERVATIONS

EUGENE ZISKIND, M D

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AND

EDGAR F MAUER, M D

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The primary purpose of this paper is to record the subsequent progress and necropsy observations in the case of hyperinsulinism previously reported on¹ In addition, mention will be made of special studies in regard to the phosphate content of the blood, psychomotor tests and the sugar content and pressure of the spinal fluid

REPORT OF CASE

A short résumé of the previous report is presented

A youth aged 19 was admitted in a state of coma to the Los Angeles County General Hospital on Sept 8, 1930 For eighteen months he had had spells of weakness, headache, trembling and mental confusion which occurred at about noon The sugar content of the blood was found to be 40 mg per hundred cubic centimeters He remained in coma for ten days Right hemiparesis, anomia, aphasia and apraxia and right hemianopia were present The hemiparesis disappeared after three weeks, the aphasia, at the end of six weeks, and the hemianopsia, in ten weeks Subsequent to the withholding of food the patient had a whole train of hypoglycemic symptoms associated with a fall in the sugar content of the blood, on one occasion as low as 28 mg per hundred cubic centimeters Abdominal exploration of the pancreas by one of us (W B) on March 26, 1931, revealed no abnormalities Part of the tail and body of this organ were removed The tissue was found to be entirely normal The clinical course of the disease was unaltered

Subsequent Clinical Course—Between October 1931 and March 1932 the patient was under the care of Dr Howard West During that time attempts were made to control the hypoglycemia by means of a diet high in fat and low in carbohydrate, but this proved unsatisfactory A second operation was performed by one of us (W B) on Jan 26, 1933, and 22 Gm of the body of the pancreas was removed No abnormality was detected in the tissue, and again no change in the clinical course was observed

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1 Ziskind, E Hyperinsulinism Report of a Case of Spontaneous Hypoglycemia, with Studies in Dextrose Tolerance, Arch Int Med 52 76 (July) 1933

Further efforts with medicinal remedies were made. Ephedrine, $\frac{1}{8}$ to $\frac{1}{4}$ grain (25 to 50 mg) three times a day over a period of two weeks, was ineffective in producing any substantial change in the sugar level of the blood. It was previously shown that epinephrine constantly produced a rise in the sugar content of blood in this patient. Strom-Olsen² has demonstrated an increase and prolongation of the elevation of the sugar content of the blood in the dextrose tolerance test when epinephrine is administered simultaneously. In the hope of diminishing the number of feedings, epinephrine, 5 minims (0.3 cc) four times a day for five days and 10 minims (6 cc) four times a day for ten days, was administered subcutaneously, but the patient had just as many spells as before. As adrenal cortex extract has been reported to elevate the sugar content of the blood,³ 2 cc of a commercial extract of adrenal cortex⁴ was given by hypodermic injection, but it caused no rise in the sugar content, and 1 cc doses twice daily for ten days produced no salutary effects. Larger doses were not available because of the expensiveness of this medicine.

A preparation of the anterior lobe of the hypophysis,⁵ 2 cc by hypodermic injection, was given three times a week between October 3 and November 21 without materially affecting the sugar content of the blood. Wilder⁶ previously recorded improvement in a case of hypoglycemia by treatment with a product of the anterior lobe of the pituitary gland.

Sodium dinitrophenol is said to produce a loss of weight, a rise in the sugar content of the blood and depletion of the glycogen stores.⁷ Since the patient's weight had gradually increased in three years from 120 to 250 pounds (54.5 to 113.5 Kg), any method to prevent a further increase in weight, particularly when associated with a rise in the sugar content of the blood and a depletion of the glycogen stores, appeared desirable. Sodium dinitrophenol was given in doses of $1\frac{1}{2}$ to $4\frac{1}{2}$ grains (97 to 292 mg) during most of January and on through September 1934. On one occasion (February 19 to 21) the temperature rose to 40.9 C (105.6 F) rectally. Discontinuation of the medicine immediately resulted in a return of the temperature to normal. It was possible to renew the doses at the previous level without untoward symptoms, except for the appearance of a cutaneous rash on July 31 and September 25. The rash disappeared in both instances after the cessation of treatment. The drug was discontinued after the second appearance of the rash. During the nine months of treatment with dinitrophenol the patient gained only 6 pounds (3 Kg). This represented a definite retardation of his previously rapidly increasing obesity. It is difficult to say whether or not the hypoglycemic manifestations were at all affected by the therapy.

2 Strom-Olsen, R. The Blood Sugar Curve in Mental Cases, *Lancet* **1** 128 (Jan 16) 1932.

3 Britton, S. W., and Silvet, H. Effects of Cortico-Adrenal Extract on Carbohydrate Metabolism in Normal Animals, *Am J Physiol* **100** 693 (May) 1932.

4 The preparation used was eschatin.

5 The preparation used was antuitrin.

6 Wilder, J. Ein neues hypophysares Krankheitsbild. Die hypophysare Spontanhypoglykämie, *Deutsche Ztschr f Nervenhe* **112** 192, 1930.

7 Hall, V. E., Field, J., II, Sahyun, M., Cutting, W. C., and Tainter, M. L. Carbohydrate Metabolism, Respiration and Circulation in Animals with Basal Metabolism Heightened with Dinitrophenol. *Am J Physiol* **106** 432 (Nov) 1933.

The effect of the drug in this connection appears to us to warrant its further trial in other cases

Throughout this entire period the patient had numerous hypoglycemic episodes. He had learned what the early prodromal symptoms were and would immediately take orange juice or some other carbohydrate. Control of the hypoglycemia in this manner proved more adequate than any method we could devise. During the night he rarely exceeded the three hour interval without food before hypoglycemic symptoms became apparent.

On Nov 9, 1934, the patient appeared to be as well as usual and conversed normally with the nurse at 11 45 p m. Ten minutes later he was found dead in bed, lying with his face buried in the pillow and his left arm reaching out for a bottle of orange juice on a nearby table. He was markedly cyanotic and was thought to have smothered in a hypoglycemic attack.

Gross Postmortem Observations—The essential observations at necropsy, performed two hours after death, were as follows. The body was that of a markedly obese man about 25 years of age. The head and neck were extremely cyanotic.

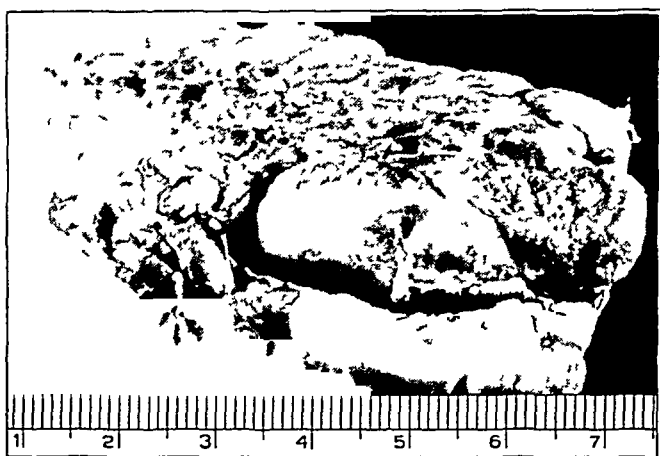


Fig 1—Remaining pancreas, showing section through the tumor

The pupils were round, dilated and equal. There were several well healed surgical scars in the wall of the upper portion of the abdomen. The abdominal panniculus averaged 8 cm in thickness.

The pancreas presented the major pathologic picture. Only the head and a portion of the body of the pancreas remained. It measured 8 by 5 by 2.5 cm and weighed 50 Gm. Its appearance and consistency were normal except for an ovoid mass situated in the posterior surface of the distal portion of the body. The tumor measured 2.5 by 2 by 2 cm (fig 1). Its external surface consisted of gray-white fibrous material which formed an incomplete capsule and sharply demarcated the mass from the pancreatic parenchyma in approximately three fourths of its surface. The remaining portion was in contact with the surrounding pancreatic tissue but did not appear to invade it. On section the capsule of the tumor measured 2 to 3 mm in thickness. The central portion of the tumor was pink-gray, firm and infiltrated by dense strands of connective tissue which appeared to be growing in from the capsule.

The thymus measured 5 by 3 by 2 cm and was beefy red and soft. The testes and the pituitary, thyroid and parathyroid glands were normal, as were the adrenal glands, although the latter were somewhat increased in size. The brain was of

average size for an adult. The dura was normal. There were moderate pial injection and milky thickening of the leptomeninges over the anterior portion of the hemispheres. The brain surfaces were markedly cyanotic. The cerebellar tonsils showed a slight degree of herniation, and the uncinatæ gyri showed minor grooving, but there was no flattening of the cerebral convolutions. The blood vessels at the base of the brain were soft and thin walled. Coronal sections revealed symmetrical ventricles which were not dilated. The brain stem and cerebellum were without morbid change.

The heart weighed 380 Gm. There were numerous small petechial hemorrhages in the parietal pericardium. The left ventricular wall averaged 2 cm. in thickness. The aorta was hypoplastic. The diaphragm was at the level of the third rib on the right and the fourth rib on the left. The pleural surfaces were thin and glistening and contained a few small petechial hemorrhages. The trachea and bronchi were filled with bloody mucous material. The right lung weighed 475 Gm. and was grossly normal except for moderate hyperemia in its basal portions. The left lung weighed 425 Gm. and was similar in appearance.

The peritoneum was smooth and moist. The omentum was large, it contained a great deal of fat and was adherent to the anterior parietal peritoneum. The stomach contained a moderate amount of partially digested food. The small intestine was filled with yellow chyme. The solitary and agminate lymph follicles of the small and large intestines were hyperplastic. The liver weighed 3,300 Gm. The external and cut surfaces were smooth and pale yellow to brown. The lobules were not clearly demarcated, the central portions appeared pale yellow. The gall-bladder, biliary passages and portal system were normal. The spleen was firm and weighed 340 Gm. On section it presented an acutely congested deep purple-red surface in which numerous closely packed hyperplastic malpighian corpuscles were seen. The kidneys together weighed 425 Gm. The capsules stripped readily from smooth, extremely cyanotic cortical surfaces. On section the renal architecture appeared normal, but the entire parenchyma was intensely cyanotic. The renal pelvis, ureters, bladder, prostate and external genitalia were normal. The skeletal system presented no abnormality.

Histopathologic Observations—The pancreatic parenchyma, except for the tumor, showed no microscopic abnormality. The islets appeared normal in size and number. The tissue immediately adjacent to the tumor, aside from slight compression, revealed no significant change. There was no evidence of infiltration by tumor cells (fig 2A).

The capsule of the tumor consisted of dense collagenous connective tissue from which heavy strands projected into the central portions. One of these divided the mass into two unequal parts. Finer projections produced irregular lobulation (fig 2B).

The capsule was infiltrated by slender irregular strands and large sheets of cells similar to those of which the tumor mass was composed. These will be described presently (fig 3A).

Ducts of various sizes also were seen in the capsule. Some of them were markedly dilated, as though obstructed, others appeared compressed. In one area the duct epithelium appeared continuous with the tumor tissue (fig 3B).

Bensley, studying the material of Womack and his associates,⁸ worked out the various stages of islet cell tumors, using as criteria the vascular accommodation

8 Womack, N. A., Gnagi, W. B., and Graham, Evarts A. Adenoma of the Islands of Langerhans with Hypoglycemia, J. A. M. A. 97:831 (Sept. 19) 1931.

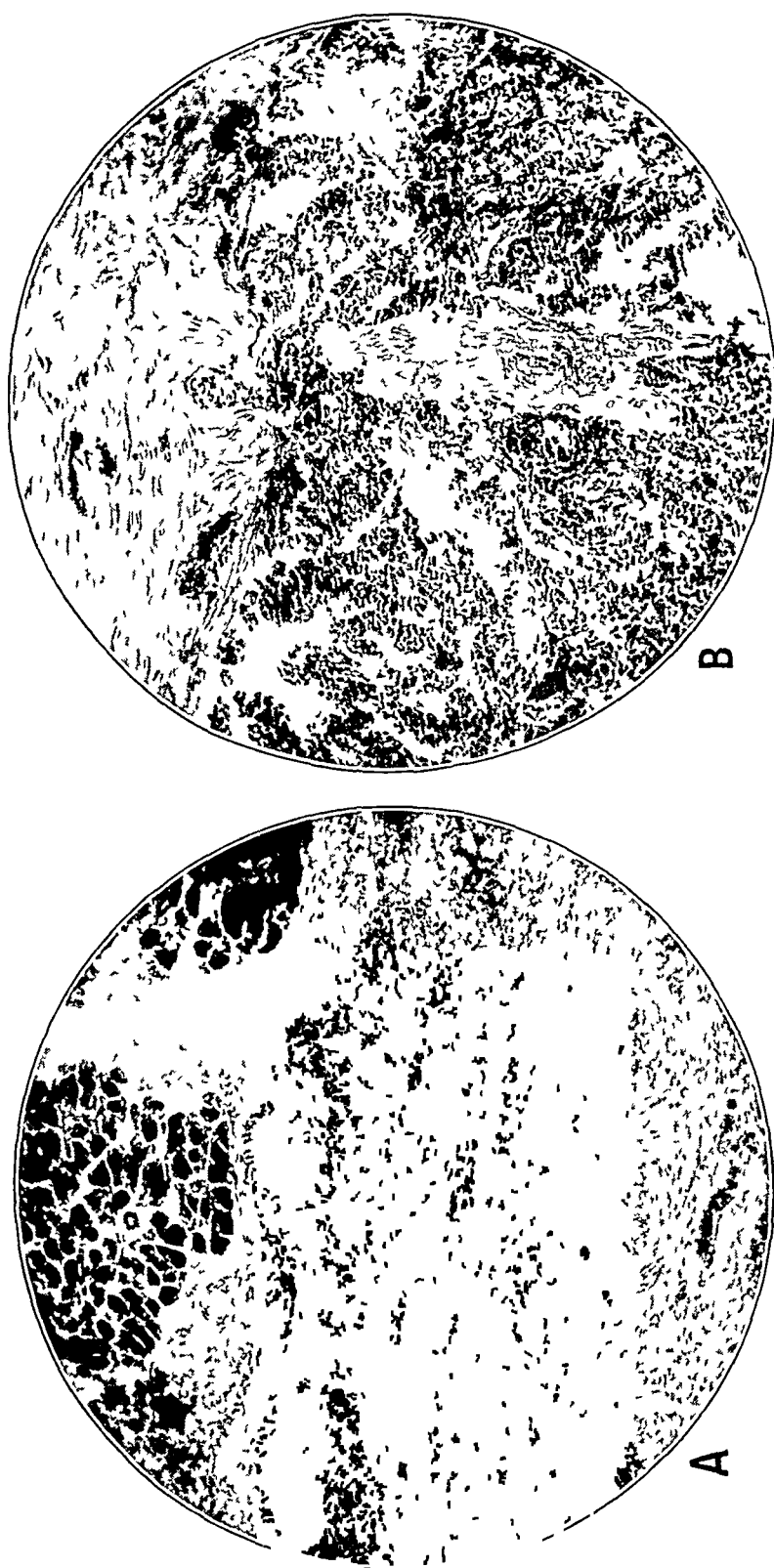


Fig 2—A, the capsule with adjacent pancreas, B, the tumor adjacent to the capsule ($\times 65$)

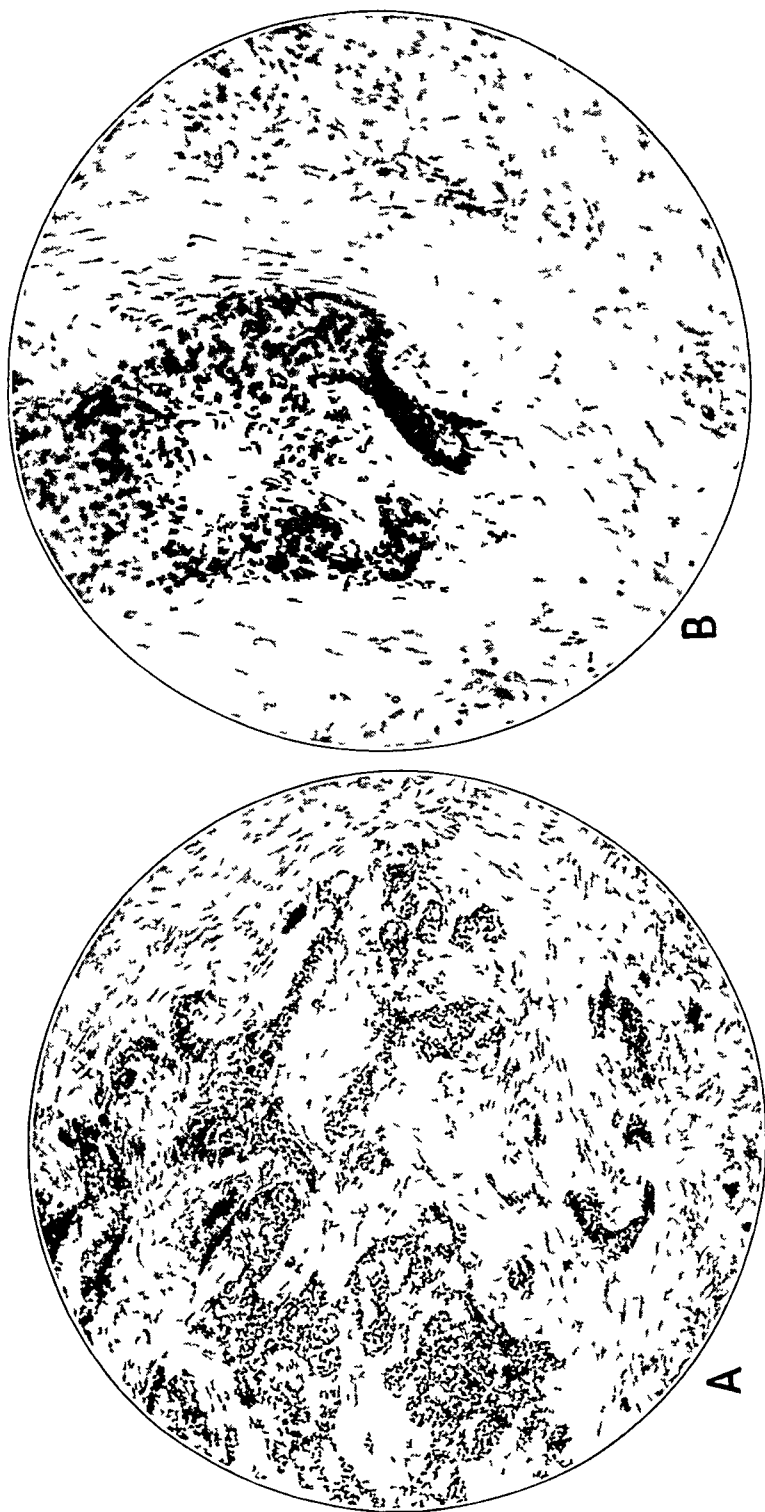


Fig 3 —A, the capsule infiltrated by tumor cells ($\times 65$), B, a pancreatic duct with tumor cells ($\times 180$)

and degree of fibrosis. He demonstrated that in the early stages there was an intimate cell-capillary relationship resembling that of the normal pancreatic islet and that, as growth progressed, the parenchymal proliferation exceeded the vascular growth. Also, as the stage of tumor development advanced, there was a corresponding tendency to separation of the epithelial structures from the capillaries by deposition of increasing amounts of perivascular connective tissue. Degeneration and necrosis were observed in the presumably older portions of the tumors. O'Leary and Womack,⁹ studying the material with which Bensley worked and two additional tumors, confirmed these observations.

In the portions of the tumor studied in our case we did not find anything comparable to the earliest stages of tumor growth described by Bensley. In no



Fig 4—The general pattern of the tumor

area did the cell-vascular accommodation appear as intimate as in the normal islet. The earliest stage of development noted in this tumor was in one area adjacent to the capsule, where the tissue resembled in its general appearance a huge island of Langerhans (fig 4). This consisted of interlacing cords of epithelial cells, from 2 to 4 cells in thickness, separated by a fairly rich capillary network. Even these vessels, however, were invested with a thin layer of connective tissue.

Elsewhere the tumor was in a more advanced stage of development and for the most part consisted of thick cell cords and masses, separated by dense bands of connective tissue. In this region the vascular supply was less profuse, and large cell masses were interposed between widely separated capillaries. In those areas the deposition of connective tissue along the capillaries and around the

⁹ O'Leary, J. L., and Womack, N. Histology of Adenoma of the Islets of Langerhans, *Arch Path* **17** 291 (March) 1934.

arterioles and small arteries was striking. This feature was even more marked around the larger blood vessels just within the capsule. A few cells throughout the tumor appeared degenerated, adjacent to the larger vessels with thickened peripheral connective tissue were small areas of cellular degeneration with hemorrhage. No hyalinization was observed.

Fixed in Zenker's solution (prepared according to the original formula, with acetic acid) and stained with hematoxylin and eosin and with Mallory's aniline-acid fuchsin stain, the component cells of this tumor resembled the cells of the islands of Langerhans. They were, however, somewhat larger than the cells comprising the individual islets observed elsewhere in the pancreas. They were polygonal where they were in contact, round or ovoid where discrete. The cell boundaries were distinct. With hematoxylin and eosin stain the cytoplasm was distinctly eosinophilic and in most instances agranular. Occasional cells showed fine granularity. The nuclei stained deeply, were fairly large, round to ovoid and of uniform size and shape and contained irregular chromatin accumulations. Some of the cells contained 2 mature nuclei. Rare bar-shaped mitoses were present.

With fixation in Zenker's solution and Mallory's aniline-acid fuchsin stain the cytoplasm had an appearance suggesting granularity, but no specific granules were seen. In some cells the granular cytoplasm was dull red, in others it was distinctly blue. Most of the cells contained large, spherical amorphous cytoplasmic masses which stained a deep brick red. They were as large as or larger than the nucleus, in some instances they were seemingly attached to the nuclear membrane, and in others, lying free in the cytoplasm.

Tissue fixed in Zenker's solution was sent to Professor Bensley, who applied his neutral gentian stain and the Bowie and the Mallory azan stains. He was unable to identify any specific granules but commented on the granular appearance of the cytoplasm. This, he said, may have been a coagulation phenomenon. With the azan method, he said, "practically every epithelial cell contains a mass of hyaline material as large as the nucleus. This stains distinctly blue. The nature of it, of course, is unknown."

Unfortunately for the studying of the granularity of the cytoplasm our material was fixed in the standard Zenker's solution, containing acetic acid, rather than in the more appropriate form of Zenker's solution in which solution of formaldehyde U S P is used instead of the acetic acid. On the technic of fixation of tissues for a study of the granules, Lane¹⁰ remarked "It is of the utmost importance that acetic acid be carefully avoided, as I have found that even a few drops of this acid, after repeated trials with numerous fluids containing acetic acid, were enough to vitiate the entire work." Bowie,¹¹ however, obtained good results with fixation in solution containing acetic acid.

We are therefore at a loss to explain the significance of the absence of specific granules in this tumor. They may have been dissolved out by the acetic acid, or they may have been absent initially. Regarding this question Professor Bensley stated in a personal communication that the absence of specific granules "does not mean that the tumor did not cause the hypoglycemia, since these tumors

10 Lane, M. A. Cytology of the Areas of Langerhans, *Am J Anat* **7** 409, 1907.

11 Bowie, D. J. Cytologic Studies of the Islets of Langerhans in a Teleost, *Neomancus Griseus*, *Anat Rec* **29** 57, 1924.

do not all behave alike in relation to stains and in particular the granules often fail to stain like either A or B granules with neutral gentian and Bowie's stains. In a neoplasm one must expect all grades of deviation from the normal."

We do not feel that this tumor was malignant. Partially encapsulated tumors of this type have been described⁹ in which there was no evidence of malignancy. In this tumor there was no infiltration into the adjacent pancreatic tissue, nor was there extension into the blood vessels. Symptoms of hypoglycemia were present for almost six years, and laboratory confirmation was obtained more than four years before death occurred, and yet there were no metastases.

The thyroid gland was normal. Serial sections of the entire pituitary gland were examined and reported on by Dr. E. M. Butt as without significant deviation from the normal. The microscopic architecture of the thymus was normal. The Hassall corpuscles were almost uniformly hyalinized, although a few with cellular structure remained. The blood vessels were moderately congested. Hematoxylin and eosin and a stain for myelin sheaths in sections from the motor cortex of the brain, the angular gyrus and optic radiations revealed no pathologic condition. The myocardium was normal. In the lungs there were small areas of acute emphysema, with rupture of the alveolar walls. Adjacent to these were small patches of atelectasis. Many alveoli were filled with fluid transudate, while others contained small extravasations of blood. The vessels were moderately engorged. The polygonal cells in all portions of the hepatic lobule contained large amounts of fat, in many cases apparently completely replacing the cytoplasm. There was a moderate degree of periportal round cell infiltration. The splenic pulp was acutely congested with blood. The malpighian corpuscles were hyperplastic. The kidney was normal except for slight cloudy swelling of the tubular epithelium. There was marked engorgement of the entire vascular tree. The adrenal glands were normal. In the testis there was active spermatogenesis, but there appeared to be fewer interstitial cells than normal.

Sections of the liver stained for glycogen by the Best carmine method revealed large amounts of glycogen in the polygonal cells, an observation in agreement with presumable hyperinsulinism. Sections of the myocardium and kidney so stained revealed no glycogen granules.

Of incidental interest in this case, although in all probability of no immediate significance, was the presence of a so-called thymicolymphatic constitution, as evidenced by the persistence of the thymus, the hyperplasia of the lymphoid tissues of the spleen and intestine, the enlargement of the intra-abdominal lymph nodes and the hypoplasia of the aorta and the slight enlargement of the adrenal glands.

It is probable that the immediate cause of death in this case was asphyxia, the culmination of a hypoglycemic attack. Evidences of oxygen deprivation were the extreme cyanosis of the head and neck, the brain surfaces and the kidneys, the well marked vascular engorgement of the thoracic and abdominal viscera, the petechial hemorrhages in the pericardium and pleurae, and the presence of acute emphysema and atelectasis in the lungs.

Summary of the Pathologic Observations—A tumor of the pancreatic islet cells was present which resembled in structure other tumors described in the literature. Specific granules were not seen, and a possible explanation for this is offered. Excessive glycogen stores in the liver corresponded with a presumable increase in the secretion of insulin.

CHARACTER OF THE HYPOGLYCEMIC ATTACKS

The hypoglycemic attacks in this case were numerous and varied. Frequently initial symptoms were hunger, weakness, anxiety, twitching of the right hand or right side of the face and numbness of the right hand. The patient utilized these symptoms as warnings and drank orange juice, which almost always gave rapid relief. Occasionally a convulsion occurred without any premonitory symptoms. In mild attacks, besides the aforementioned initial indications, there occurred nausea, vomiting, headache, drowsiness, trembling, perspiration, facetiousness, pugnacity, ataxia and loss of speech. Objectively, there were pallor, coldness of the extremities, tremor, profuse perspiration, dilatation of the pupils, a subnormal temperature and an increase in the pulse pressure. Tachycardia was present so much of the time (although no cardiac lesion was demonstrable) that it could not be utilized as an indication of hypoglycemia. More severe symptoms were aphasia, hemiparesis, confusion, involuntary laughing, crying and singing, delusions, hallucinations, convulsions, and coma. All of these were observed at different times. The type of symptom was not entirely dependent on the level of the blood sugar. Occasionally a low value for blood sugar (e g, 32 mg per hundred cubic centimeters) was recorded without any subjective or objective abnormality. However, in the presence of symptoms hypoglycemia was always found. A few of these symptoms call for more detailed analysis.

It is interesting that frequently there were minor personality changes incident to the lowered glyceemic state. The patient, who ordinarily was quiet, pleasant and cooperative, would become stubborn or facetious and at times mean and surly, while apparently retaining all his normal capacities. It was repeatedly necessary to demonstrate his response to carbohydrate in these instances in order to convince the nurses in attendance that he was not wilfully uncooperative. For a short period this patient was cared for at the Los Angeles County Farm, where his ailment was considered largely hysterical. Here orange juice was withheld. He was returned to the hospital in a state of acute psychosis and for one week showed definite hallucinations and delusions.

The convulsive episodes were of particular interest. These also varied from time to time. Usually they were preceded by a long or short period during which the aforementioned hypoglycemic manifestations were present. As a matter of fact, the convulsions were usually the summation of increasing hypoglycemic effects and would in all probability have been more frequent if the falling level of the blood sugar had not been curbed early in its downward course. The preliminary period might be a few hours, and again the convulsions might occur without any premonitory symptom. The attacks varied also in their totality. Numbness of the right hand, twitching of the right hand

on right eyelid, right-sided jacksonian seizures and generalized convulsions, with or without residual hemiparesis and the Babinski reflex phenomena, each occurred as isolated manifestations. Almost always the patient regained consciousness rapidly after a convulsion, at which time the level of the blood sugar would have returned to normal.

The hypoglycemic symptoms occurred most frequently in the morning, when there had been the longest interval after eating. The nurses' notes frequently indicated "profuse diaphoresis" during the night, and the patient was often confused on being aroused for breakfast.

The clinical picture presented during hypoglycemia was no different from that observed in many other instances of hyperinsulinism. May we stress again the variability of symptoms from time to time and the occurrence of spells remote from the preceding meal and emphasize such special symptoms as the profuse perspiration, the subnormal temperature and the convulsive phenomena present in all types of qualitative and quantitative variants?

SPECIAL STUDIES

1 *Inorganic Phosphates of the Blood Serum*—Injection of insulin in a normal subject causes a diminution in the content of organic phosphates in the blood as well as in the sugar content¹². These changes coincide with the modern interpretations of muscle metabolism. Hexose phosphate is considered to be an intermediary product in muscle metabolism. Insulin, in storing muscle glycogen, is thought to convert blood sugar and blood phosphates into hexose phosphate, hence the diminution in the phosphate and sugar contents of the blood after the injection of insulin. Similarly, a high carbohydrate feeding also depresses the phosphate content, presumably by inducing the secretion of insulin. During muscular activity this process is reversed, glycogen breaks down to hexose phosphate and then to lactic acid, with the release of phosphates into the blood stream. Corresponding with this concept, Harrop found the phosphate level elevated subsequent to strychnine convulsions in rabbits.

The content of sugar and phosphate in the blood was determined in five instances at variable periods after breakfast. The patient had breakfast at 7 a. m., and usually dextrose was given in some form at 8 o'clock to assure a high level for blood sugar when tests were carried out. Blood sugar determinations were made by the Benedict method¹³ and blood phosphate determinations by the method of Benedict and Theis¹⁴. In two tests the values for the calcium, the total protein, the volume and the carbon dioxide-combining power also were obtained. The results are shown in table 1.

12 Harrop, G. A., Jr., and Benedict, E. M. The Participation of Inorganic Substances in Carbohydrate Metabolism, *J. Biol. Chem.* **59** 683, 1924.

13 Benedict, S. R. The Estimation of Sugar in Blood and Normal Urine, *J. Biol. Chem.* **68** 759 (June) 1926.

14 Benedict, S. R., and Theis, R. C. A Modification of the Molybdic Method for the Determination of Inorganic Phosphorus in Serum, *J. Biol. Chem.* **61** 63, 1924.

TABLE 1—Serial Readings of the Blood Sugar and Serum Inorganic Phosphate Values

Date	Tests	Data										Comment
		9 30 a m	10 30 a m	11 00 a m	11 45 a m							
9/12/33	Blood sugar, mg per 100 cc	91 0	58 0	51 0	41 0							7 a m, breakfast
	Blood phosphates, mg per 100 cc	3 8	5 5	5 5	7 6							8 a m, 500 cc of orange juice
												9 30 a m, 250 cc of orange juice
9/15/33		11 15 a m	11 40 a m	12 45 p m	1 35 p m	2 20 p m						Convulsion in the morning
	Blood sugar, mg per 100 cc	178 0	104 0	40 0	33 0	37 0						10 a m, 1,000 cc of orange juice, 1 cc of epinephrine, hypodermically
	Blood phosphates, mg per 100 cc	3 8	3 8	4 5	4 5	4 5						
9/19/33		9 00 a m	9 40 a m	10 10 a m	10 40 a m	11 10 a m	11 35 a m	1 30 p m				7 14 a m, breakfast
	Blood sugar, mg per 100 cc	73 0	64 0	63 0	52 0	52 0	41 0	45 0				11 40 a m, 750 cc of orange juice, 10 cc of
	Blood phosphates, mg per 100 cc	3 5	3 7		3 7	3 7	4 4	4 2				50 per cent solution of dextrose intravenously
		12 7	12 2		12 8	13 0	12 8	13 0				12 m, two sandwiches and milk
	Blood calcium, mg per 100 cc											
9/22/33		8 50 a m	11 15 a m	1 20 p m								7 a m, breakfast
	Blood sugar, mg per 100 cc	164 0	47 0	116 0								8 a m, 500 cc of orange juice
	Blood phosphates, mg per 100 cc	4 0	5 3	5 1								
9/29/33	Blood calcium, mg per 100 cc	13 0	13 0	13 0								
		9 15 a m	10 20 a m	11 15 a m	11 30 a m	1 45 p m						7 a m, breakfast
	Blood sugar, mg per 100 cc	50 0	42 0	C*	68 0	53 0						8 a m, 500 cc of orange juice
	Blood phosphates, mg per 100 cc	3 5	3 5		5 6	4 1						

* Convulsion

Whenever the sugar level was low, the level for inorganic phosphates rose. In one instance after a convulsion there was a marked increase in the phosphate level. The values for the calcium, the total protein, the volume and the carbon dioxide-combining power did not vary with the different levels for blood sugar. The rise in the phosphate content in this patient with hyperinsulinism was in contrast to the results of the injection of insulin. With insulin or with insulin plus dextrose,¹⁵ a fall in the phosphate level manifests itself within the first hour and may persist for only from one to three hours. Since initial determinations of the sugar content in our studies were obtained more than one hour after the taking of dextrose, an initial drop in the phosphate content may have been missed. These studies will therefore need to be repeated before our findings can be properly evaluated. The conditions of our tests differed from the insulin experiments in at least two other particulars which may be significant. First, there was present in our patient presumably an excessive amount of insulin, continuously or at least for prolonged periods, in place of transient hyperinsulinism following the injection of insulin. Second because of the absolute necessity for frequent feedings, our tests were not performed in the postabsorptive state. As stated, our data are difficult to evaluate. The finding of interest is that the phosphate content of the blood was high and increasing when the sugar content was low and falling. Further studies in regard to this matter on patients with hyperinsulinism may prove of value.

2 Psychomotor Reactions—As hypoglycemia produces such marked changes in mental functions, it was desirable to note at what stage the earliest psychic manifestations appeared.

The procedure adopted consisted in withholding food and obtaining blood sugar determinations, noting hypoglycemic symptoms and recording reactions to special tests at repeated intervals. Three trials were employed at each test. In the association tests five words were submitted, and opposite responses were requested. Scoring was done on the basis of correct responses without consideration of the time element. Strength was indicated by the hand grip, as measured with the dynamometer. The average was taken from two trials each with the right and left hands. Speed was measured by the number of revolutions on a finger counter during the first thirty seconds. The number of revolutions during the next thirty seconds was taken as a measure of endurance. The progressive fall in the sugar content of the blood limits the time and hence the number of tests which can be made at any one level. The results are indicated in table 2.

The earliest hypoglycemic effect on the psychomotor reactions was a decrease in the auditory memory span for sentences, except once, when defective association processes were noted sooner. Impairment of mathematical ability and disorientation occurred at later lower hypo-

¹⁵ Ellsworth, R. Secondary Alterations in Total Serum Calcium After the Administration of Glucose and Insulin, *J Clin Investigation* 8 139 (Feb.) 1930

TABLE 2—Results of Psychomotor Tests at Various Hypoglycemic Levels

Hypoglycemic Signs and Symptoms																		
Motor Tests										Blood Pressure, Mm of Mercury								
Date	Time	Blood Sugar, Mg per 100 Cc	Memory Span*			Association Test	Speed, Revolutions	Endurance, Revolutions	Pupils	Tremor	Perspiration	Pulse Rate	Systolic Diastolic		Other Symptoms			
			Digits	Words	Sentences								Systolic	Diastolic				
8/22/33	10 30 a m	51	3	3 ²	2 ¹				0	0	0	108			Vagant stare			
	11 00 a m	48	3	2	1 ¹				Moderate dilatation	+	0	108						
8/29/33	11 30 a m	36	3?	0	0				Moderate dilatation	++	—	120			Twitchings in right arm, mannerisms (facial)			
	12 00 m	65	4 ²	4 ³	2				0	0	0	120						
8/29/33	9 45 a m	47	3				28		0	++	+	120			Clearing of throat per severation, mannerisms, stereotypy			
	10 30 a m	43	3				33		0	+++	0	120						
9/12/33	11 00 a m	42	1				0	0	Dilated	++++	0	144			Irresponsible, poor cooperation			
	11 45 a m	142	5				101	105	0	+	+	132						
9/12/33	9 30 a m	91	5		3	5	65†	47	Moderate dilatation	0	?	120	130	100	Weak			
	10 20 a m	58	5		2	5	89	64	Dilated	0	?	112	156	104				
	11 00 a m	51	4		2	5	103	47	Dilated	+	0	84	144	90				
	11 45 a m	41	3		1	1	24†	65	Dilated	++	0	118	158	108				
9/15/33	11 15 a m	178	5		3 ¹	5	128	100	0	+	0	144	130	80	Apathetic cleary throat			
	11 45 a m	104	5		3	5	129	104	0	+	0	148	130	96				
	12 45 p m	40	4		1	P§	113	90	0	+++	+	130	146	100				
	1 35 p m	33	4		1	3	113	96	0	++	0	128	156	104				
	2 30 p m	37	3		1	P§	87	68	0	+++	+	120	132	90				
																Drowsy, blinking, gross tremor, mannerisms stereotyped speech		
9/19/33	9 00 a m	73	4		3	5	127	112	4 mm	?	?	120	146	105	Nervous			
	9 40 a m	64	5		3	5	132	90	4 mm	?	0	120	146	100				
	10 10 a m	61	4		2	2	117	96	5 mm	+	0	114	158	110				
	10 40 a m	52	4		3 ²	1	110	83	5 mm	+	0	118	140	108				
11 10 a m	52	3		1	0	138	0	0	5 mm	+++	0	132	152	120	Apathetic, stereotyped actions			
	11 35 a m	41	0		0	0	0	0	0	—	0					Confused, catatonic		
1 30 p m	45	5		4		185	129	97	0	+	0	120	126	80	Restlessness, generalized twitchings			
															Thrashing about			

* The superior numbers indicate the number of tests

† The patient had not learned the technique

‡ Poor cooperation

§ P indicates perseveration

glycemic levels. Abnormalities in the psychic functions suggested a depression of the sugar level before tremor, perspiration, dilatation of the pupils or other general hypoglycemic symptoms were evident. Since the patient had a rapid pulse at all times, tachycardia could not be correlated with hypoglycemia in this case. The psychologic functions manifested impairment at higher glycemic levels than did the motor. Speed and endurance diminished with increasing hypoglycemia, these were more sensitive than tests for strength.

This study reveals the early vulnerability of auditory verbal memory. Our tests indicate that the earliest interference is with psychic rather than with muscular functions. Similar results were obtained in a study by Dashiell¹⁶ on a diabetic patient receiving insulin, although no readings for the blood sugar were taken and the work on the whole was qualitative rather than quantitative. The early involvement of memory processes during hypoglycemia calls to mind the frequency of impairment of memory in the organic syndromes in psychiatric disorders.

3 Sugar Content and Pressure of Spinal Fluid—The spinal fluid changes with variations in the concentration of sugar in the blood stream. With the induction of hyperglycemia, the spinal fluid pressure becomes depressed, with hypoglycemia, it becomes elevated¹⁷. The spinal fluid, according to a well substantiated theory, is a "dialysate in osmotic and hydrostatic equilibrium with the blood plasma"¹⁸. This would call for modifications in the spinal fluid pressure on the basis of the concentration of sugar not only in the blood but also in the spinal fluid. Normally the content of sugar in the spinal fluid is from 50 to 70 per cent of that in the blood and varies in the same direction as the sugar content of the blood. A change in the sugar content of the blood is followed by a latent period of from two to five hours before the equilibrium between the sugar in the blood and that in the spinal fluid is reestablished, apparently the period of time required for permeability adjustments through the hemato-encephalic barrier¹⁹. The great fluctua-

16 Dashiell, J. F. Variations in Psycho-Motor Efficiency in a Diabetic with Changes in the Blood Sugar Level, *J. Comp. Psychol.* **10** 189, 1930.

17 Weed, L. H., and McKibben, P. S. Pressure Changes in the Cerebrospinal Fluid Following Intravenous Injection of Solutions of Various Concentrations, *Am. J. Physiol.* **48** 512, 1919.

18 Fremont-Smith, F., Thomas, G. W., Dailey, M. E., and Carroll, M. P. The Equilibrium Between Cerebrospinal Fluid and Blood Plasma, *Brain* **54** 303, 1931.

19 Gregersen, M. I., and Wright, L. Effect of Intravenous Injection of Sucrose and Glucose upon Reducing Power of Cerebrospinal Fluid, Before and After Hydrolysis, *Am. J. Physiol.* **112** 97 (May) 1935. Goodwin, G. M., and Shelley, H. J. The Sugar Content of the Cerebrospinal Fluid and Its Relation to the Blood Sugar, *Arch. Int. Med.* **35** 242 (Feb.) 1925.

tions of the level of the blood sugar in cases of hyperinsulinism offer an opportunity for checking many of these physiologic principles

Therefore, determinations of the spinal fluid pressure and the sugar content of the blood and spinal fluid were obtained at varying levels of the blood sugar after food had been withheld. The spinal fluid pressure was always taken with the patient in a horizontal position. The results are presented in table 3. Before these results can be evaluated, it is necessary to take into consideration some of the experimental difficulties

TABLE 3—*Values for the Sugar Content of the Blood and Spinal Fluid and the Spinal Fluid Pressures at Various Hypoglycemic Levels*

Date	Time	Blood Sugar, Mg per 100 Cc	Spinal Fluid Sugar, Mg per 100 Cc	Spinal Fluid Pressure, Mm of Mercury	Symptoms
11/ 5/31		88	75	250	
3/29/32		41	40		
3/16/33	9 00 a m	111			None
	10 15 a m	81	83	147*	None
	11 30 a m	47	66	205	None
	12 30 p m	46			None
	1 30 p m	46	37	262	Drowsy, restless, singing incoherently
3/30/33	8 30 a m	111			
	9 00 a m	146			
	11 00 a m	85	93	175†	
	11 30 a m	53	83	150	
	12 00 m	49	77	150	
	12 30 p m	39	63	150	
	1 00 p m	38	50		1 15 p m, tremor, blinking of eyes
	1 30 p m	48	48		1 30 p m, smacking of lips, clearing of throat, numbness of feet, restlessness
	2 00 p m	38	42		2 00 p m, singing, whining, face tiousness, perspiring, disoriented (did not know date), could not multiply 7×9 or add 2+3

* Spinal puncture at 10 15 a m, needle left in place until 11 30 a m, 5 cc of fluid removed at 10 and 11 30 a m. Second puncture performed at 1 30 p m, this fluid was slightly blood tinged throughout, the bloody contamination probably occurred at the time of withdrawal of the needle at 11 30, since the puncture wound then bled freely and the subcutaneous tissue became distended.

† Spinal puncture at 11 a m, needle left in situ until 1 p m. Needle reinserted at 1 30 p m and removed at 2 p m, 5 cc of fluid withdrawn for the first four sugar determinations, 3 cc for subsequent tests.

involved. These apply only to serial observations. First, the withdrawal of spinal fluid for sugar determinations markedly lowers the spinal fluid pressure. Hence, combined serial readings for the sugar content and the pressure of the spinal fluid are not possible, and the values for the spinal fluid pressures obtained after the initial reading must be discounted in our studies. When, however, the spinal fluid pressure rises at subsequent readings (as in the study of Nov 16, 1933) the increase in pressure must be accepted as indicating the general direction, though it cannot be the absolute value. Apparently the rise was sufficiently great to overshadow the loss due to the withdrawal of spinal fluid, or the interval was long enough to permit replacement of the

lost fluid. Second, leakage at the site of puncture is a factor which may affect subsequent pressure readings. This necessitates leaving the needle in place throughout the entire study. Third, the needle as a foreign body probably excites a local inflammatory reaction when in place for any prolonged period, and this may elevate the pressure. Finally, there is a possibility that the spinal puncture itself may alter the permeability of the hemato-encephalic barrier. Both of the latter possibilities require normal controls and cannot be properly evaluated in this study. Despite these considerations, the initial readings are all valid. The subsequent determinations of the sugar content of the blood and spinal fluid also represent the true state of affairs, unless alterations in the permeability of the hemato-encephalic barrier were induced. Although subsequent readings of the spinal fluid pressure have definite limitations as to their absolute accuracy, the general trend or direction can be accepted for the readings on March 16, 1933, for the reasons already given.

The following conclusions from this study appear warranted. Low values for blood sugar or hypoglycemic states are associated with an increase or elevation of the spinal fluid pressures. A definite latent period exists between the time of a change in the value for blood sugar and restoration of the equilibrium of the blood sugar-spinal fluid sugar ratio. This is apparent from the results in table 3, and since the fall in the value for blood sugar was rapid in this patient and the latent period was relatively long, it leads to the paradoxical situation in which the sugar content of the spinal fluid is even higher than that of the blood during part of the period of readjustment. It is of interest that during the study of March 16, 1933, the sugar content of the blood remained stationary at 47 mg per hundred cubic centimeters for two hours. During that time the sugar content of the spinal fluid dropped from 66 to 37 mg per hundred cubic centimeters, and hypoglycemic symptoms appeared only toward the end of this interval. Since low values for the sugar content of venous blood may exist without symptoms, the foregoing observation suggested a possible correlation between low sugar levels for the spinal fluid and the development of "hypoglycemic" symptoms. This thought was rudely disturbed by the observation in another patient with hyperinsulinism²⁰ that hypoglycemic symptoms were present when the sugar level of the blood was low but that of the spinal fluid was high, higher than the level for the blood.

4 *Intradermal Saline Test*—The intradermal saline test of McClure and Aldrich²¹ was performed at different levels of hypoglycemia

20 Ziskind, E, and Bailey, W. Hyperinsulinism. Report of a Second Case with Anatomic Findings, to be published.

21 McClure, W. B., and Aldrich, C. A. Time Required for Disappearance of Intradermally Injected Salt Solution, *J. A. M. A.* **81** 293 (July 28) 1923.

Absorption of the wheals always required more than an hour, which is longer than the normal rate

The test indicates that no state of dehydration exists in the skin, although Drabkin and Shilkret²² have demonstrated anhydremia after an injection of insulin. If anything, the tissues of our patient may have been in a state of increased hydration. This observation is based on only an isolated uncontrolled experiment and is presented as such.

5 Effect of Mental Work on Sugar Content of Blood—Modern researches indicate that there is no storage of dextrose in the brain and that the nervous system is directly dependent on the sugar and lactic acid in the blood for its fuel supply. In hypoglycemic states the adequacy of this supply is interfered with. If mental work utilizes energy from the combustion of carbohydrates, such an increased demand for fuel might result in an early precipitation of hypoglycemic symptoms in a patient with hyperinsulinism.

TABLE 4—*Results of Intradermal Saline Test*

Time when wheals were made	9 15 a m	9 55 a m	10 30 a m *
Blood sugar, mg. per 100 cc	50		42
Disappearance of wheals	1 hour plus	1 hour plus	1 hour plus

* Convulsions occurred at 11 15 a m

To test this, our patient performed additions for thirty minutes at six different sessions. Blood sugar determinations were made before and after each test period and also for thirty minute control periods preceding and following the test. The development of hypoglycemic symptoms also was recorded.

The results were inconclusive. The mental work did not produce a sufficient increase in the consumption of dextrose by the brain to be reflected in a recognizable depression of the sugar level of the blood.

SUMMARY AND CONCLUSIONS

A report is made of the clinical course of a patient with hyperinsulinism who was observed for four years (most of the time in a hospital). Necropsy revealed an adenoma of the pancreatic islets which had not been discovered at two previous pancreatic resections.

Dinitrophenol had a retarding effect on the increasing obesity. This result and the physiologic indications for the drug in these cases would indicate its further trial for symptomatic relief, particularly in hypoglycemia not amenable to surgical intervention, were it not for the severe toxic effects sometimes noted when this drug is used.

The variability in the hypoglycemic attacks is stressed.

²² Drabkin, D. L., and Shilkret, R. Insulin Anhydremia, *Am J Physiol* 83: 141, 1927.

A rise in the content of inorganic phosphates in the blood was discovered during the hypoglycemia present in our patient after the ingestion of dextrose. Further studies are indicated, since a fall in the phosphate content is reported in insulin hypoglycemia.

Impairment of psychologic functions, e. g., an effect on the memory span, was among the earliest signs of insulin hypoglycemia.

The spinal fluid pressure is elevated in a hypoglycemic state. In our patient the latent period between the drop in the sugar content of the blood and the ultimate fall in the sugar content of the spinal fluid was so long that the level in the spinal fluid during part of this interval was at a higher level than that in the blood.

The intradermal saline test did not reveal a state of dehydration in the skin during the hypoglycemic phase.

The effect of mental work on the level of the blood sugar was tested, but the results were inconclusive.

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ROLE OF THE ARTERIES IN THE PERIPHERAL RESISTANCE OF HYPERTENSION AND RELATED STATES

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It seems established that arterial hypertension must be due to increased peripheral resistance, since the other factors which are involved in the maintenance of blood pressure—cardiac output,¹ volume of the blood² and viscosity of the blood³—have been proved to be normal in patients with hypertension. Since it has recently been shown that the blood flow in the arm is normal in hypertensive patients,⁴ it is probable that the increase in resistance is widespread, affecting all parts of the body and not merely, as had been suggested, the splanchnic or other localized areas. Moreover the increased resistance must be due to hypertonicity of the vessels, i e, a functional constriction, not due to a structural narrowing, since relaxation of these hypertensive vessels can be obtained.^{4a} The evidence concerning the exact cause of the increased peripheral resistance is still somewhat negative, since it has

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2 Linder, G C, Lundsgaard, C, Van Slyke, D D, and Stillman, S. Changes in the Volume of Plasma and the Absolute Amount of Plasma Proteins in Nephritis, *J Exper Med* **39** 921 (June) 1924.

3 (a) Austrian, C R. The Viscosity of the Blood in Health and Disease, *Bull Johns Hopkins Hosp* **22** 9 (Jan) 1911. (b) Friedman, B, and Prinzmetal, M. Vasomotor Effects of Blood in Patients with Hypertension, *Proc Soc Exper Biol & Med* **34** 543 (May) 1936.

4 (a) Prinzmetal, M, and Wilson, C. The Nature of the Peripheral Resistance in Arterial Hypertension with Special Reference to the Vasomotor System, *J Clin Investigation* **15** 63 (Jan) 1936. (b) Pickering, G W. Peripheral Resistance in Persistent Arterial Hypertension, *Clin Sc* **2** 209 (May) 1936.

been shown not to be of neurogenic origin⁴ and not to be due to any pressor substance having a direct effect on the vessels⁵. Evidence has recently been obtained which indicates that a pressor substance normally present in the kidneys is probably increased in dogs with experimentally produced hypertension⁶ and in patients with essential and "renal" hypertension^{6b}.

The present paper deals with the question of which part of the vascular bed is concerned with the increase in peripheral resistance. It is conceivable that narrowing might occur in any of the four main subdivisions of the peripheral circulation—arteries, arterioles, capillaries or veins. It has, however, been known for some time that there is no rise in venous pressure in hypertensive conditions, and it has more recently been shown that capillary pressure also is normal⁷. For these and other reasons it seems probable that neither the veins nor the capillaries are responsible for the rise in blood pressure.

On theoretical grounds, since the arterioles normally contribute by far the major part of the peripheral resistance, it seems probable that constriction of these vessels may be responsible for the tremendous rise in resistance in hypertension. The finding by Weiss and Ellis⁸ that arteriolar pressure is increased in hypertensive conditions supports this contention. Whether or not the larger arteries also are abnormally constricted remains uncertain.

There appears to be no doubt that spasm of the retinal vessels may occur in patients with eclampsia, malignant hypertension and nephritis, and Moschcowitz⁹ has reported that in certain cases of acute nephritis there is an increased tonus of the radial artery. More recently, Weiss and his co-workers¹⁰ have shown that even when there is a high pulse

5 Pickering, G. W. The Effect of Introducing Blood from Patients with Essential Hypertension into Other Human Subjects, *Clin. Sc.* **2** 185 (May) 1936. Friedman and Prinzmetal^{3b}.

6 (a) Harrison, T. R., Blalock, A., and Mason, M. F. Effects on Blood Pressure of Injection of Kidney Extracts of Dogs with Renal Hypertension, *Proc. Soc. Exper. Biol. & Med.* **35** 38 (Oct.) 1936. (b) Prinzmetal, M., and Friedman, B. Pressor Effects of Kidney Extracts from Patients and Dogs with Hypertension, *ibid.* **35** 122 (Oct.) 1936.

7 Ellis, L. B., and Weiss, Soma. The Measurement of Capillary Pressure Under Natural Conditions and After Arteriolar Dilatation in Normal Subjects and in Patients with Arterial Hypertension and with Arteriosclerosis, *J. Clin. Investigation* **8** 47 (Dec.) 1929.

8 Weiss and Ellis^{1c}. Ellis and Weiss⁷.

9 Moschcowitz, E. Pseudo, or Transient, Arteriosclerosis, *J. A. M. A.* **90** 1526 (May 12) 1928.

10 Weiss, Soma, Haynes, F. W., and Shore, R. The Relation of Arterial Pulse Pressure to the Hemodynamics of Arterial Hypertension, *Am. Heart J.* **11** 402 (April) 1936.

pressure the cardiac output of hypertensive patients remains essentially normal. According to Wiggers,¹¹ who worked with an artificial circulation an increased pulse pressure with a normal cardiac output indicates a diminution of arterial elasticity. Weiss therefore concluded that the hypertension must be due not only to increased resistance in the arterioles but also to physical changes in the arterial wall. The attempt by the same authors to show roentgenographically that the arteries themselves become narrowed in hypertensive conditions was inconclusive. This result might have been foretold, since by Poiseuille's law the pressure varies inversely with the fourth power of the radius, and consequently even the greatest possible rise in blood pressure would be due to a variation in diameter of such a minute dimension that it would be well within the limits of error of observation.

METHOD

Since, according to Poiseuille's law, the pressure in the vascular system is proportional to the resistance, the gradient, or fall, in pressure in passing from large to small arteries, through arterioles to capillaries and veins, is determined by the resistance in the different parts of the system. It seemed, therefore, that a study of pressure in large and in small arteries of normal and of hypertensive persons might reveal whether there is any change in the pressure gradient with a rise in blood pressure.

If the pressure gradient from large to small arteries should become steeper with the rise in systolic pressure in hypertension, it would point to an increased resistance in the larger arteries. If, on the other hand, the gradient should be lessened or should remain unchanged in hypertension, it would indicate that the increased resistance is on the arteriolar side, not in the arteries.

We therefore determined the blood pressure in the brachial artery by the usual auscultatory method and in the digital artery by a modification of the method of Gartner.¹²

The subjects included twenty-five persons with normal, fifty-one with raised and fourteen with low blood pressure. Of the hypertensive patients, nine had malignant, 10 secondary, or "renal," and thirty-two "benign" hypertension. We were careful to exclude subjects having congestive heart failure, aortic insufficiency or severe anemia.

Observations were also made in cases of peripheral vascular abnormalities of various types, including thrombo-angitis obliterans, thrombosis of the brachial

11 Wiggers, C. J. Physical and Physiological Aspects of Arteriosclerosis and Hypertension, *Ann Int Med* 6:12 (July) 1932.

12 Gartner, G. Ueber einen neuen Blutdruckmesser (Tonometer), *Wien med Wchnschr* 49:1412 (July 22) 1899. Formijne, P. Investigation of the Patency of Peripheral Arteries, *Am Heart J* 10:1 (Oct) 1934.

artery and sclerodactylia, and in one case of pheochromocytoma associated with paroxysmal hypertension

Details of Method—For determining the pressure in the digital artery we used a Gartner capsule,¹² applying it to one of the digits, preferably the third (middle) digit. According to this method the finger is inserted into a hollow metal cuff or cylinder (fig. 1) made of appropriate size and shape to fit the finger loosely. This cuff is lined with a thin rubber membrane (part of a finger-cot), tied firmly over the two ends. The interior of this capsule is connected by means of a side tube with the mercury manometer of an ordinary blood pressure apparatus. To make the determination the finger is first rendered anemic by pushing on to it, from tip to base, a rather tight rubber ring, the capsule is placed over the middle phalanx of the finger, and the pressure is raised until it is higher than that expected in the digital artery. The rubber ring is then cut so that the blood flows into the finger up to the capsule, and the pressure in the capsule is slowly reduced until, at a certain pressure, the tip of the finger beyond the cuff is suddenly filled with blood. The pressure at which this flushing occurs is assumed to be the systolic pressure in the digital artery.

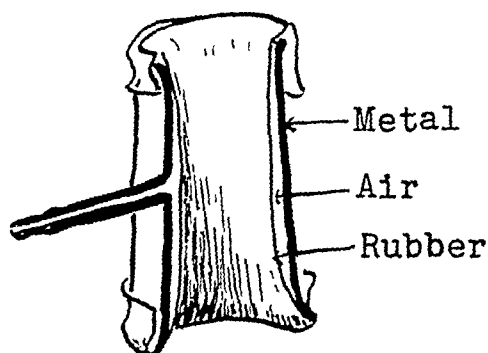


Fig. 1—Section through the capsule of Gartner (adapted from Formijne)

Both the brachial and the digital pressure were taken with the patient in the recumbent position, with the usual precautions of having the patient rest before the determination and keeping the artery under investigation at the level of the heart.

Determinations of brachial pressure were made at least twice—at the beginning and at the end of each series of observations—and usually more frequently, alternating with the determinations of digital pressure. The number of determinations of the digital pressure varied from five to ten, depending on the degree of variation between the different observations.

No significant differences in pressure could be observed in the different fingers or with natural variations in the temperature of the skin of the hand.

RESULTS

The results of our observations are summarized in tables 1 to 5 and are shown graphically in figures 2 and 3.

For the twenty-five control patients (table 1) with a normal blood pressure we found an average brachial systolic pressure of 124 mm of mercury and a brachial diastolic pressure of 73 mm, giving a pulse pressure of 50 mm. The average digital systolic pressure was 95 mm.

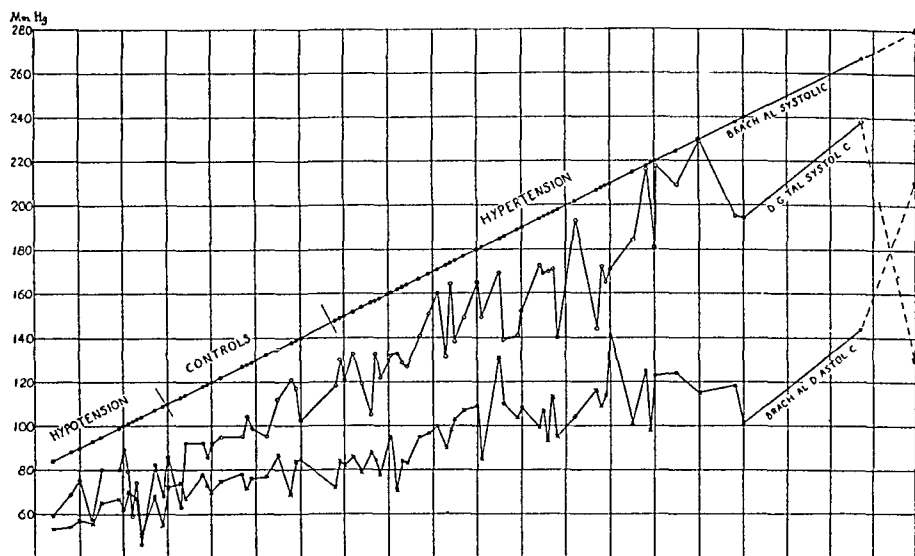


Fig 2—Chart showing the brachial systolic, digital systolic and brachial diastolic pressures of seventy-four persons, including hypotensive and hypertensive patients and controls. The last values at the right are for a patient with pheochromocytoma.

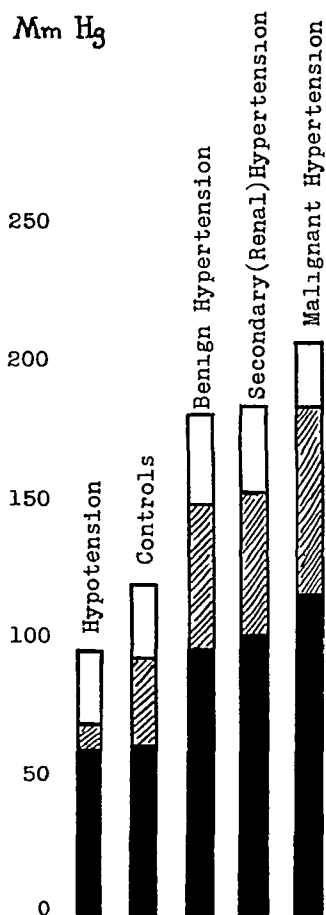


Fig 3—Chart of the blood pressure readings. The white column indicates the brachial systolic pressure, the shaded column, the digital systolic pressure, and the black column, the brachial diastolic pressure.

that is, the average difference between the brachial and the digital systolic pressure was 29 mm, thus agreeing with the results of earlier workers¹³

For the fifty-one hypertensive patients (table 2) our figures showed an average brachial systolic pressure of 188 mm, a brachial diastolic pressure of 102 mm (that is, a pulse pressure of 86 mm) and an average digital systolic pressure of 159 mm. The average difference between the brachial and the digital systolic pressure was 29 mm. The pressure gradient therefore remained practically unchanged.

If among the hypertensive patients we consider only the group of patients with malignant hypertension (table 2C), we find some indication

TABLE 1—Data for Twenty-Five Controls

Case No	Age	Sex	Pressure, Mm of Mercury					Clinical Diagnosis
			Brachial Systolic	Brachial Diastolic	Pulse	Digital Systolic	Brachial-Digital Gradient	
1a	27	M	140	85	55	102	38	Normal
1b	27	M	133	77	56	95	38	Normal
1c	27	M	119	73	46	86	31	Normal
3	28	M	128	72	56	104	24	Hemophilia
4	17	M	110	73	36	92	18	Convalescent from rheumatic fever
5	54	M	120	71	41	93	27	Obstructive jaundice
6	40	M	110	76	34	70	40	Convalescent from ileitis
8	24	F	135	87	48	112	23	Nonmalignant bronchial bleeding
10	32	M	127	83	44	87	41	Convalescent from acute nephritis
13	45	F	110	68	38	96	14	Normal
14	14	M	120	70	50	86	34	Convalescent from lobar pneumonia
19	44	M	127	80	47	96	33	Convalescent from diabetes, hepatic cirrhosis and acute nephritis
20	26	M	113	74	39	63	50	Convalescent
23	30	M	127	71	56	102	25	Cough, hemoptysis
27a	25	M	129	74	55	99	30	Normal
27b	25	M	120	70	50	94	26	Normal
27c	25	M	118	70	48	84	34	Normal
28	55	M	114	67	47	95	19	Convalescent from bronchopneumonia
36	42	M	110	68	42	75	35	Convalescent from bronchiectasis, afebrile
45b	35	M	118	86	32	101	17	Convalescent from acute nephritis
55	56	M	139	84	55	117	22	No arteriosclerosis
56	48	F	148	72	76	118	30	Surgical menopause
58b	16	F	114	20	94	89	25	Convalescent acute nephritis
62	52	F	138	69	69	121	17	Normal
86	35	F	122	75	47	95	27	Normal pressure on right side, left side, obliterative vascular disease
Averages			124	73	50	95	29	

that the digital pressure tends to approach the brachial pressure. The patients with malignant hypertension, with a brachial systolic average of 210 mm, had a diastolic pressure of 118 mm, a pulse pressure of 92 mm and an average digital systolic pressure of 186 mm. The digital pressure was therefore only 24 mm below the brachial pressure, and there was a slight decrease in the average pressure gradient.

As will be seen from figure 2, for three patients with hypertension with extremely high brachial pressure we actually found digital pressure

13 Cohn, A. E., and Lundsgaard, C. A Study of the Blood Pressure by the Method of Gartner, Especially in Patients Suffering from Fibrillation of the Auricles, *J. Exper. Med.* **27**: 487 (April) 1918. Wishart, G. M. Blood-Pressure Observations with a New Type of Oscillometer, *Clin. Sc.* **1**: 159 (Dec.) 1933.

TABLE 2—Data for Fifty-One Hypertensive Patients

Case No	Age	Sex	Pressure, Mm of Mercury					Clinical Diagnosis
			Brachial Systolic	Brachial Diastolic	Pulse	Digital Systolic	Brachial Digital Gradient	
A Benign hypertension (32 patients)								
17	36	F	161	96	65	129	32	Mild hypertension
18a	45	M	156	88	68	106	50	Postoperative chronic nephritis
24a	44	M	202	104	98	194	8	{End stage of nephrosclerosis cardiovascular
24b	44	M	196	94	102	170	26	{ disease, renal insufficiency
25	46	M	175	104	71	138	37	Gastric ulcer
29	23	F	174	95	79	153	21	Conversion hysteria
33	48	M	174	102	72	166	8	
34	63	M	194	89	105	152	42	Arteriosclerosis +++
39	57	F	193	100	98	146	52	Menopause
40	63	F	216	101	115	184	32	Arteriosclerosis +
31	54	F	198	91	107	134	64	Moderate arteriosclerosis
42	62	F	209	114	95	165	44	
43	65	F	240	102	138	194	46	Arteriosclerosis ++
47	50	F	154	79	77	119	35	Menopause
48	58	M	167	89	78	147	20	Arteriosclerosis ++
50	60	F	177	107	70	149	28	Arteriosclerosis +
51	52	M	162	71	91	133	29	No arteriosclerosis
52	44	F	180	109	71	165	15	
53	54	F	167	101	67	134	33	Arteriosclerosis ++ and menopause
57	49	F	267	144	123	239	28	Severe hypertension, menopause
63	37	M	173	90	83	131	42	No arteriosclerosis
21	64	F	164	84	80	126	38	
64	53	M	208	109	99	172	36	Severe hypertension, menopause
66	46	M	181	85	96	149	32	Arteriosclerosis ++
67	54	F	150	82	68	121	29	Surgical menopause
68	68	F	220	126	94	165	55	Arteriosclerosis ++
70	60	F	152	87	65	134	18	Arteriosclerosis +
71	56	F	158	78	80	122	36	Auricular fibrillation
72	55	F	171	100	71	160	11	Arteriosclerosis and lymphatic leukemia
73	47	F	190	108	82	153	37	Menopause
79	68	F	194	110	84	193	1	Arteriosclerosis +++
92	60	M	152	86	66	133	19	Bronchial asthma
Averages			184	98	86	152	32	
B Secondary (renal) nephritis (10 patients)								
26a	47	M	207	116	91	144	63	Renal colic
26b	47	M	186	110	76	138	48	Renal colic
30	52	F	225	124	101	210	15	Hydronephritic contracted kidney
44	50	M	197	113	84	172	25	Subacute glomerular nephritis
45a	35	M	195	106	89	169	26	Acute diffuse glomerular nephritis
53a	16	F	163	84	79	130	33	Acute glomerular nephritis
59	67	F	219	98	121	175	44	Arteriosclerosis +
65	38	F	161	94	67	141	20	Chronic pyelonephritis
75	40	F	149	84	65	130	19	Chronic glomerular nephritis
77	27	F	169	97	72	151	18	Acute glomerular nephritis
Averages			187	103	85	156	31	
C Malignant hypertension (9 patients)								
15a	42	M	218	125	93	216	2	Essential hypertension arteriosclerosis +
15b	42	M	220	120	100	218	2	Essential hypertension, arteriosclerosis +
16	46	F	230	115	115	229	1	Malignant nephrosclerosis, fingers cold and cyanotic
38	29	M	238	135	103	184	54	Malignant hypertension
69	68	F	189	104	85	141	48	Essential hypertension
76	46	F	185	131	54	169	26	Marked retinal changes, postpneumonia fall in blood pressure
78	48	F	210	141	69	171	39	Early malignant hypertension
46a	60	F	238	102	136	214	24	Coronary sclerosis convalescent from cystitis
46b	60	F	157	85	72	133	24	Coronary sclerosis convalescent from cystitis blood pressure fell after infection
Averages			210	118	92	186	24	
Averages of all 3 groups of hypertensive patients			188	102	86	159	29	

only 1 or 2 mm below the brachial pressure, a remarkable reduction of pressure gradient. Our fourteen patients with hypotension (table 3) showed an average brachial systolic pressure of 98 mm, an average diastolic pressure of 61 mm and hence a pulse pressure of 37 mm. The average digital pressure of these patients was 71 mm, which was 27 mm lower than the brachial systolic pressure.

With this method of determining the digital blood pressure, no diastolic reading can be obtained to compare with the brachial diastolic pressure. It may, however, be of interest to note that, whereas in the controls the average diastolic pressure was found to be approximately half way between the brachial systolic and the brachial diastolic pressure,

TABLE 3—Data for Fourteen Hypotensive Patients

Case No	Age	Sex	Pressure, Mm of Mercury					Clinical Diagnosis
			Brachial Systolic	Brachial Diastolic	Pulse	Digital Systolic	Brachial Digital Gradient	
7	44	F	103	67	36	74	29	Convalescent from pneumonia
11	45	F	93	56	37	37	36	Ulcerative colitis and arteriosclerosis ++
12	25	F	95	65	30	80	15	Normal
22	25	M	107	68	39	82	25	Arrested pulmonary tuberculosis
32		F	99	64	35	89	10	Pleurisy with effusion
35	40	M	102	63	39	59	43	Convalescent from renal cortical abscess
81	58	M	104	50	54	46	58	Emphysema
82	38	M	100	62	38	90	10	Bronchiectasis
84	24	F	84	53	31	59	25	Chronic vaginal fistula
85	39	F	88	54	34	69	19	Convalescent from pyelonephritis
88	55	M	90	58	32	75	15	Coronary heart disease
89	47	M	101	70	31	79	22	Coronary heart disease
90	50	M	99	74	25	71	28	Coronary heart disease
91	33	M	109	55	65	68	41	Chronic ulcerative colitis
Averages			98	61	37	71	27	

in the hypertensive patients the average digital systolic pressure rose with the brachial systolic pressure far above the brachial diastolic pressure. For the hypotensive patients the reverse was found to be true, the digital systolic pressure more nearly approaching the brachial diastolic pressure. In fact, in three patients, each of whom had a brachial systolic pressure below 112 mm, the digital systolic pressure actually fell below the brachial diastolic pressure.

These results are summarized graphically in figure 3, where the average pressures obtained for the three groups of hypertensive patients are compared with those for the hypotensive patients and the controls.

It seems certain, therefore, that in hypertension there is no increase in the pressure gradient between brachial and digital arteries, in fact in cases of very high blood pressure this pressure gradient may even be reduced.

Brachial-Digital Gradient in Paroxysmal Hypertension—We were fortunate at the time to have a patient with paroxysmal hypertension due to pheochromocytoma. During attacks the patient's face and extremities became cold and blanched, indicating arterial spasm. Large amounts of epinephrine could be demonstrated in the blood during a hypertensive attack but not after operation for removal of the adenal tumor. The operation also caused a disappearance of the hypertension and effected a complete cure. The complete details of this case are reported elsewhere¹⁴

TABLE 4—Data for Woman (Case 74) Aged Twenty-Six with Pheochromocytoma

		Pressure, Mm of Mercury				
		Brachial Systolic	Brachial Diastolic	Pulse	Digital Systolic	Brachial Digital Gradient
Before operation						
Resting		184	129	55	141	43
Minutes after exercise	1	230	190	90	130	150
	3	230	160	120	170	110
	5	266	158	108	176	90
	7	220	148	72	154	66
Resting		192	133	59	165	27
Minutes after exercise	1	230	180	100	130	150
	3	255	160	95	180	75
	5	220	150	70	166	54
	7	200	140	60	156	44
After operation (removal of pheochromocytoma)						
Resting		133	96	156	90	43

TABLE 5—Data for Four Patients with Obliterative Vascular Disease

			Pressure, Mm of Mercury					Clinical Diagnosis
Case No	Age	Sex	Brachial Systolic	Brachial Diastolic	Pulse	Digital Systolic	Brachial Digital Gradient	
37	52	M	103	65	38	27	76	Thrombo angitis obliterans
61	37	F	107	70	37	27	80	Sclerodactylia
80	53	M	104	50	54	29	75	Thrombosis of brachial artery
87	35	F	122	75	47	58	64	Thrombo angitis obliterans
Averages			109	65	44	35	74	

It was thought that a patient with this type of disorder would serve as a control for our observations, because it is well known that epinephrine causes constriction of arteries as well as of arterioles. This patient was particularly useful as a control because we were able to make determinations of her blood pressure during attacks of hyper-

14 Beer, E., King, F. H., and Prinzmetal, M. Pheochromocytoma with Demonstration of Pressor (Adrenalin) Substance in the Blood Preoperatively During Hypertensive Crises, to be published

tension due to epinephrinemia and also after restoration of the normal blood pressure by removal of the tumor. It was found that exercise precipitated an attack in this case.

Table 4 demonstrates the results of the two sets of observations: the first, those obtained during paroxysmal hypertension induced by exercise before operation and, later, those of a similar study after operation. It will be seen that during the paroxysmal hypertension induced by exercise the brachial systolic pressure rose to 280 mm while the digital systolic pressure actually fell from the resting level of 141 mm to 130 mm. This resulted in a brachial-digital gradient of 150 mm, as contrasted with the 30 mm gradient of chronic hypertension.

After operation, when the patient's blood pressure returned to a more nearly normal level, the abnormally steep gradient was found to disappear. With a brachial systolic pressure of 133 mm there was a digital systolic pressure of 90 mm giving a gradient of only 43 mm.

The fact that for this patient with obvious arterial spasm the pressure gradient became tremendously steep supports our contention that in ordinary hypertension, in which the gradient is either normal or slightly reduced, there is no arterial constriction.

Brachial-Digital Gradient in Obliterative Vascular Disease—Table 5 shows the readings for four patients with obliterative vascular disease, each of whom had obstruction of the blood flow through the medium-sized arteries. The figures clearly show that the fall in pressure between the brachial and the digital arteries was much greater than in normal persons or in the hypertensive or hypotensive patients. Thus with an average brachial systolic pressure of 109 mm, there was an average digital systolic pressure of only 35 mm, that is, a brachial-digital gradient of 74 mm.

Like the patient with pheochromocytoma, this group of patients showed a marked contrast to our other patients, the data indicating that obstruction of the arteries, whether due to spasm, as in pheochromocytoma, or to organic changes, as in obliterative vascular disease, causes an increased gradient in the fall in pressure between the brachial and the digital artery.

COMMENT

For reasons stated previously, it seems to us that the fact that in ordinary hypertension there is no increase in the brachial-digital gradient must mean that the arteries do not play an important rôle in the production of the high peripheral resistance. The increased resistance must therefore occur in vessels smaller than the digital arteries.

The observation of spasm of the retinal arteries in certain types of hypertension is not incompatible with our results, since the vessels are

considerably smaller than the digital arteries, being more nearly of the order of arterioles

No apparent relationship was observed between the degree of arteriosclerosis determined by palpation of the radial artery and the brachial-digital gradient, some patients having marked arteriosclerosis and a small gradient and vice versa. This is in agreement with the blood flow previously recorded for persons with thickened radial arteries.¹⁴

In the three cases of more serious obliterative vascular disease it is of interest that the digital pressures were all closely alike, being 27, 27, and 29 mm, respectively. Since, according to Landis,¹⁵ this is approximately the same as the normal pressures found on the arterial side of the capillaries, it suggests that it may approximate the lowest pressure at which an adequate capillary flow may be maintained.

It is noteworthy that the patient (case 87) having the least degree of ischemia had the highest digital pressure. These results suggest the possibility that study of the brachial-digital relationship may prove to be a useful index to the degree of obstruction in the arteries.

SUMMARY AND CONCLUSIONS

A study was made of the brachial-digital pressure gradient for subjects with low, normal and high blood pressure.

Similar studies were also made for one patient with paroxysmal hypertension due to adrenal pheochromocytoma and for four patients with obstructive vascular disease.

The average brachial-digital pressure gradient for patients with chronic hypertension was found to be approximately the same as for those with a normal or a low blood pressure. For three patients with a very high blood pressure there was a notable reduction in gradient.

Since there is no increase in the gradient in hypertension it is concluded that there is no increased resistance in the arteries larger than the digital arteries.

For the patient with pheochromocytoma with epinephrinemia the pressure gradient was markedly increased, indicating constriction of arteries larger than the digital arteries.

For four patients with obliterative vascular disease the pressure gradient was also increased, owing to obstruction in the arteries resulting from organic changes.

This increase in pressure gradient, contrasted with the normal or perhaps decreased gradient of chronic hypertension, supports the view that in hypertension there is no increased resistance in the larger arteries.

15 Landis, E. M. Capillary Pressure and Capillary Permeability, *Physiol. Rev.* **14** 404 (July) 1934.

HYDATID DISEASE

CLINICAL, LABORATORY AND ROENTGENOGRAPHIC OBSERVATIONS

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The history of hydatid disease goes back to ancient times. The Jews were familiar with it in their sacrificial slaughter of animals, and the Talmud makes definite reference to it. Hippocrates (460-379 B C) wrote of "livers filled with water." References to the disease were made also by Galen (139-200 A D) and later by various writers during the Middle Ages, including Rhazes (860-932 A D).

At first the condition was considered to be due to morbid processes, such as broken-down lymph glands or collections of pus. Later, however, other investigators brought to light information which led to an understanding of the parasitic nature of *Taenia echinococcus*. Leuchart, in 1867, described his observations made on artificially infected pigs. However, it was the work of the Italian scientist Francesco Redi (1626-1694) that established the animal origin of the cyst. Thomas, an Australian, published a book in the 1880's. Déve, of Rouen, France, had compiled a long list of notable contributions that have been made to the literature since his first articles on this subject appeared in 1901. He is regarded as one of the outstanding authorities on this subject today. Dew, an Australian, published a noteworthy book on the subject in 1928.

Weinberg and Ghedini from 1906 to 1909 worked out the complement fixation test. Welsh, Chapman and Storey studied the application of the precipitin test. In 1911 Casoni first used the intradermal reaction to detect hydatid disease. Some time later Keith D. Fairley, N. Hamilton Fairley and Williams, Kellaway, and others carefully investigated the serologic tests for hydatid disease.

During the last seventy years various authors in many countries have written voluminously on the subject, until today the life cycle of the parasite and the clinical and the pathologic aspects of the disease are well understood. Naunyn, of Berlin, Krabbe, of Iceland, and authors from Central Europe and South America also have made valuable contributions on the subject.

DISTRIBUTION

Hydatid disease has been reported from all countries, and, though the disease has a universal distribution, it is found chiefly in countries

where sheep are raised, the sheep being the usual intermediary host. One of the factors necessary for the infestation of a country is that dogs have access to sheep's organs. In Australia and New Zealand, where there are roughly 13 and 15 sheep, respectively, per capita, the viscera of slaughtered sheep are frequently fed to dogs.

In Iceland, where there are approximately 2 sheep per capita and many dogs are kept to handle the sheep, Krabbe¹ found that 28 per cent of the dogs were infected, another writer there found that 1 of every 6 persons who came to autopsy was a victim of the infection. More recently the people of Iceland have been educated as to the dangers of the disease, and there has resulted a marked decrease in the rate of infection, so that in 1920 Sambon² found that the incidence was 1 in every 2,000 of the population, where formerly it had been 1 in every 40.

Other countries showing hydatid infection commonly are Algiers, Bulgaria, Roumania, certain parts of Switzerland, France, Austria, Serbia, northern Italy and Russia.

In North America, where there is 1 sheep to every 3 persons, the incidence among human beings is low. In a series of 241 reports of cases collected by Lyons³ in the United States and Canada, it was found that 91 per cent of the cases comprising the series were those of patients of foreign extraction. Osler,⁴ in a paper published in 1882, reported 66 cases of hydatid disease in human beings but stated that he was unable to find a single case of *Taenia echinococcus* infection in dogs.

During the last four decades an increasing number of sheep have been raised in the republics of Argentina and Uruguay, and this has been associated with a great increase in the incidence of hydatid infection in human beings there. According to Carbonell and Zwanck, the infestation in some parts of those countries has risen to 50 per cent of the populace. In Argentina Greenway reported that between 1910 and 1921 the incidence of hydatid infection increased at twice the rate of the increase in the population. This great increase in the incidence is due to the ignorance of the peons, their primitive method of living and the infection of water supplies.

1 Krabbe, H. *Recherches helminthologiques en Danemark et en Islande*, Copenhagen, G. E. C. Gad, 1866, p. 3.

2 Sambon, L. W. *Researches on Epidemiology of Cancer Made in Iceland and Italy*, *J. Trop. Med.* **28** 39 (Feb. 2) 1925.

3 Lyons, I. P. *The Incidence of Hydatid Disease in North America*, *Am. J. M. Sc.* **123** 124, 1902.

4 Osler, W. *On Echinococcus Disease in America*, *Am. J. M. Sc.* **84** 475, 1882.

For Australia Thomas⁵ recorded a twenty year period. During the first five year period there were 57 cases, during the second period; 112 cases, during the third period, 192 cases, and during the fourth period, which led up to 1882, 231 cases. The greatest incidence of the disease was in the southwest portion of Victoria, which has a climate not unlike that of Colorado. The incidence of the disease among Victorian hospital patients has been placed by Dew⁶ at from 1 to 294. This survey covered a period of nine years.

One thousand miles to the north of Victoria lies the State of Queensland, with its semitropical and tropical climates. Sheep raising is not so extensively carried on in Queensland as in Victoria, and the incidence of hydatid infection is lower there than in Victoria. This is due in part to the warmer climate of Queensland. The echinococcus parasite is killed by a temperature of 50 C, which frequently obtains during the summer months in some parts of Queensland.

It is of interest to note here the high incidence of infection in Australian sheep, as found by Ross in a survey made in New South Wales in 1926, when he discovered that in small abattoirs in the country 35.7 per cent of sheep slaughtered were infested with hydatid disease.⁷

LIFE CYCLE

The life cycle of *Taenia echinococcus* has been well described by various workers and therefore will be dealt with only briefly. In this infection a human being is only accidentally the intermediary host and represents a blind pocket so far as the further dissemination of the organism is concerned. The dog, wolf and jackal are the ideal definitive hosts, and they infect the food and the water supply of the herbivorous animals by fecal contamination.

The development of the parasite in man is considered to be identical with that in sheep and other intermediary hosts. Cattle are more commonly infected than sheep but are not a source of infection to dogs, for the reason that dogs are more frequently fed the viscera of sheep.

The ovum as passed by the dog is composed of a hard, striated capsule containing a hexacanth embryo. When swallowed by man, sheep, ox or pig, this ovum hatches out in the stomach or duodenum. The embryo escapes and bores its way through the wall of the stomach,

⁵ Thomas, J. D. Hydatid Disease, London, Bailliere, Tindall & Cox, 1894, p. 149.

⁶ Dew, Harold R. Hydatid Disease, Sydney, Australasian Medical Publishing Company, Ltd., 1928, p. 43.

⁷ Fairley, N. Hamilton, and Penrose, J. S. A Survey of the Incidence of Hydatid Disease in the Herbivora and Porcines of Victoria, *M. J. Australia* **2**: 640 (Nov. 24) 1928.

then, entering the radicles of the portal vein, it is swept into the liver where in the majority of cases it lodges in the lobules. After it has lodged in the liver, it may be destroyed by the reaction of antibodies. If it survives, it becomes surrounded by small mononuclear cells. After seventy-two hours eosinophil and endothelial cells appear. Dew⁶ stated that after fourteen days vesiculation occurs and the chromatin of the parasite becomes arranged in nuclear masses. Hyaline changes then take place in the cytoplasm, and fluid forms in the center of the cellular mass. At the end of three weeks the cystic follicle is visible with the unaided eye, and by the end of five months it has developed into a cyst with a diameter of 1 cm. The cyst may continue to grow, reaching a capacity as great as that of Barnett's "colossal hydatid cyst of the abdomen," from which he removed 11 gallons (42 liters) of hydatid fluid,⁸ or it may retrogress, the laminated membrane becoming wrinkled and calcareous changes frequently taking place.

The wall of the cyst is formed of two layers, ectocyst and endocyst, in addition to a protective fibrous pericyst, called the adventitia. The adventitia is formed by the tissues of the host. The germinal layer or endocyst, produces numerous brood capsules, which are attached to it by a fine pedicle and float in the fluid contained in the cyst. Within the brood capsule the scolices, or heads of the future worms, develop. A scolex is an oval body just visible with the unaided eye. This head segment of the future worm contains two rows of hooklets. In addition, there are four suckers in the head of the fully developed worm. As a result of trauma, such as needling or a blow, which threatens the vitality of the cyst, daughter cysts develop in the germinal membrane. The daughter cysts contain both scolices and brood capsules, like the mother or original cyst.

When the cyst containing viable scolices is ingested by the definitive host (dog, wolf or jackal), the scolices become attached to the walls of the small intestine and develop into complete worms, having three or four segments. The parasite measures about 5 mm in length. It lies parallel to, and is about the same size as, the villi of the small intestine. The terminal segment, containing the ova, eventually ruptures, freeing scores of ova, and it is in this way that the feces of the dog contaminate the pastures and the water supply of the herbivora.

Dévé⁹ has shown that the ova resist prolonged drying as well as soaking in water. But the period of the viability of the ova and the extremes of temperature it will withstand are not fully known.

8 Carmalt-Jones, D. W. Hydatid Disease as a Clinical Problem, *Brit. M. J.* 25 (July 6) 1929.

9 Deve, F. Echinococcose primitive experimentale, kystes hydatiques de la pleure, *Compt. rend. Soc. de biol.* 64 587, 1908.

Sn Louis Barnett¹⁰ stated the opinion that human infestation from dogs occurs more frequently through the handling of dogs than from the feeding of dogs from plates, the cause given by Baring-Gould¹¹ for the infestation in Iceland

INCIDENCE IN VARIOUS ORGANS

In man the presence of one or more cysts in some part of the body constitutes hydatid disease. The usual site of involvement is the liver, from which the peritoneum is secondarily involved. After this in frequency come the lung, muscles and cellular tissues, kidney, spleen, bones, orbit and brain.

The cases on record in the registry for hydatid disease of the Royal Australasian College of Surgeons up to the beginning of the year 1935 showed the location of cysts and the mortality to be as follows¹⁰

Site	Cases	Deaths
Liver	249	45
Other abdominal organs, mostly secondary to cysts in the liver	50	7
Lung	74	12
Muscles and fascia	21	1
Bone	14	1
Kidney	11	2
Brain	5	2
Spleen	2	1
Thyroid gland	2	
Total	428	71 (16.6%)

Dévé (quoted by Carmalt-Jones⁸) gave the following distribution for two thousand, seven hundred and twenty-seven cysts

Sites	Percentage
Liver	76.6
Lung	9.4
Muscles and cellular tissues	5.2
Kidney	2.3
Spleen	2.1
Bones	0.9
Orbit	0.2
Brain	0.6
Miscellaneous	2.2

The following figures bear out the relatively high frequency of cysts in the liver. Dévé, 76.6 per cent, Fairley,¹² 72.9 per cent, and MacLaurin,¹³ 74 per cent.

DIAGNOSIS AND LABORATORY TESTS

The only symptom of hydatid disease, as long as the cyst is intact and uninfected, may be dyspnea or a slowly growing painless tumor of

10 Barnett, L. E. Deaths from Hydatid Disease, Australian & New Zealand J. Surg. 5:205 (Jan.) 1936

11 Baring-Gould, S. Iceland, Its Scenes and Sagas, London, Smith Elder & Co., 1863, p. 58

12 Fairley, K. D. Hydatid Disease of Liver, M. J. Australia 1:177 (Feb. 23) 1924

13 MacLaurin, C. The Symptoms of Liver Hydatid, Australasian M. Gaz. 28:295 (June 21) 1909

the abdomen. But should rupture or leakage occur, anaphylaxis follows the most usual form being hydatid rash with urticarial wheals. Frequently accompanying these are irregular fever, dyspnea, cyanosis, vomiting, abdominal pain, syncope, delirium and mania. In the event that a quantity of hydatid material suddenly enters the blood stream, serious anaphylactic symptoms or even sudden death may result.

Dew⁶ has listed the symptoms of anaphylaxis according to systems as follows:

Cutaneous Pruritus, urticarial wheals, erythema and sweating

Gastro-intestinal Nausea, vomiting, diarrhea, tenesmus, abdominal pain and melena

Respiratory Tightness in the chest, spasmodic asthmatic cough, dyspnea, cyanosis, pulmonary edema and edema of the glottis

Cardiovascular Pallor, faintness, tachycardia, clammy skin, cold extremities, syncope and collapse

Nervous Agitation, convulsions, dilated pupil, delirium and coma

Previous to the advent of modern serologic and roentgenographic methods, correct diagnoses were made in about 40 per cent of cases. With the use of modern laboratory methods the percentage has risen to about 90. Three laboratory tests are of great value:

1 The precipitin test. This test, which employs the serum of the patient in prepared hydatid fluid, is accurate in 65 per cent of cases. It is of value only when used with carefully prepared controls.

2 The intradermal test. The intradermal test of Casoni is very valuable. It is carried out in a manner similar to that of the Piquet test for tuberculosis. Hydatid fluid obtained by puncture of an aseptic cyst from the lung or liver of a sheep is filtered and used for this test. When 0.3 cc of the fluid is injected intradermally into the arm of the patient, a wheal is raised that is about 8 mm in diameter. An injection of physiologic solution of sodium chloride should be used as a control. When the reaction is positive, the wheal reaches its maximum size of 4 or 5 cm in from ten to twenty minutes and is surrounded by an erythematous zone. This test, according to Fairley,¹⁴ showed positive results in 56 per cent of the cases in which there were uncomplicated cysts and in 26 per cent of the cases in which there were ruptured or suppurating cysts. The Casoni test is a useful preoperative guide, since it indicates when there has been a dangerous degree of absorption of hydatid fluid.

3 The complement fixation test. This test is specific and is dependent on a specific antibody in the serum of patients who have

14 Fairley, K. D. The Intra-Dermal Test in Hydatid Disease. A Clinical Analysis of Its Results, *M. J. Australia* 1: 472 (April 13) 1929.

absorbed hydatid antigen Fairley's technic is similar to that of the Wassermann test According to Fairley and Williams,¹⁵ in 52.4 per cent of cases there is a positive reaction preoperatively, whereas in 52.8 per cent of cases there is a positive result when there are residual or recurrent cysts

Leukocyte Count—When the common causes of eosinophilia, such as asthma, chronic disease of the skin and intestinal worms can be eliminated, a certain amount of reliance may be placed on the presence of eosinophilia In about half the cases of hydatid disease the eosinophil count is higher than normal, the upper limit of normal being placed by Fairley and Kellaway¹⁶ at 300 eosinophilic leukocytes per cubic millimeter of blood (6 per cent) Rarely, the eosinophils outnumber the neutrophils

CHARACTERISTICS OF HYDATID ELEMENTS

The hydatid fluid is clear, limpid and alkaline, with a specific gravity of from 1.008 to 1.015 It contains about 6 per cent of sodium chloride After centrifugation it should be examined for scolices and hooklets A scolex measures 160 microns in length and 115 in breadth Hooklets also may be seen, their length varying from 20 to 40 microns

ROENTGENOGRAPHY

The roentgenographic diagnosis of hydatid disease has certain limitations as well as a wide range of usefulness As in some other diseases, it is frequently necessary to place considerable weight on the clinical and other laboratory findings before the roentgenograms can be properly interpreted Modern roentgenographic and serologic methods used together make diagnosis possible in 90 per cent of cases

The problem of properly evaluating roentgenograms is variable, as different parts of the body are involved Perhaps it would be well to consider briefly the causes of the shadows under question The classic cyst has a wall composed of three layers: adventitia, ectocyst and endocyst

The adventitia, which is the pericyst, or outer layer, is made up of tissues derived from the host In some organs, such as the liver, it may be dense and capable of casting a definite shadow, in other tissues, such as the lung, it may be so thin as not to cast a shadow Again, a

15 Fairley, K. D., and Williams, F. E. The Complement Fixation Test in Hydatid Disease. An Analysis of Its Results, *J. Coll. Surgeons, Australasia* 2: 317 (March) 1930

16 Fairley, K. D., and Kellaway, C. H. The Value of Laboratory Investigations in the Diagnosis of Hydatid Infestation, *Australian & New Zealand J. Surg.* 2: 236 (Jan.) 1933

living cyst in the abdomen, for instance, may or may not cast a shadow, but should death of the cyst occur, calcium would be laid down in the adventitia, making the cyst visible

The ectocyst and its fluid contents cast a shadow, as would any localized collection of fluid

The endocyst is a fragile nucleated germinal layer lining the interior of the laminated layer. It casts no roentgenographic shadow

The roentgenographic appearance of hydatid cysts in various parts of the body will now be considered in the order of the frequency of involvement

LIVER

According to Deve, 76.6 per cent of all hydatid cysts are located in the liver. They grow silently for years, causing the patient little or no discomfort. In size they vary from that of a small pea up to that of a tennis ball. Rarely, a cyst of "colossal" size has been recorded. At times, however, the cyst may become infected and suppurate, or it may rupture into the peritoneal cavity, with widespread dissemination of brood capsules and other hydatid elements. Again, the cyst may rupture into a biliary channel, either within or without the substance of the liver, or into the gallbladder. Another common occurrence is transdiaphragmatic rupture, with emptying of the contents of the cyst into the pleural space or into a bronchus.

According to MacLaurin,¹³ in 80 per cent of cases there is involvement of only the right lobe of the liver, in 18 per cent there is involvement of the left lobe only and in 2 per cent there is involvement of both lobes. This is probably due to the fact that the right hepatic vein has a larger lumen and runs a straighter course than the left hepatic vein. This was observed by Castex, who studied the vascular system of the liver roentgenographically after the injection of opaque material into the portal vein.

Dew⁶ has stated that approximately 75 per cent of all cysts of the liver are situated either antero-inferiorly or postero-inferiorly, so that they have a tendency to extend downward into the abdominal cavity. This is of clinical importance, as the tumor is frequently rounded, cystic, smooth and not tender and moves freely with respiration. The hydatid "thrill," according to Carmalt-Jones,⁸ was noted in only 7 of over 300 cases by Barnett.

The principle roentgenographic sign of hepatic involvement is elevation of the right dome of the diaphragm, with disturbance of its normal contour. Frequently the altered contour shows segmentation. This may be due to the presence of one or more hepatic cysts in or near the upper surface of the liver, or again it may be due to compensatory hypertrophy of the hepatic cells overlying a cyst. The diaphragm

may be elevated 2 or 3 inches (5 to 8 cm) Fluoroscopic examination usually reveals diminution of the diaphragmatic excursion If there is an infected cyst near the upper surface of the liver, there may be loss of definition of the overlying portion of the diaphragm, owing to inflammation

Roentgenographically it is frequently difficult or impossible to demonstrate cysts deep in the liver or hanging from its inferior surface Some cysts growing on or projecting from the inferior surface of the liver can be demonstrated by means of a barium sulfate meal or enema, cholecystography or pyelography

For localization of hepatic hydatid cysts, it is suggested that stereoscopic films, with Claessen's heavy penetration, as for the spine, be used I have used stereoscopic films with good localization when there were broken-down calcified cysts and heavy penetration was unnecessary

Claessen¹⁷ has stated that in Iceland some calcification of the pericyst is noted in a fair percentage of cases and that by using the same penetration as for the spine the early calcification of a living cyst can be delineated The female breast sometimes casts a confusing semicircular shadow Anderson¹⁸ has stated that the perihilar basal markings of the lungs extending up from the area of involved liver are increased in density He stated that this may be due to changes in the lymphatic radicles

Differential Diagnosis—Conditions which must be considered are hepatic abscess, malignant growth, cirrhosis, syphilis and diaphragmatic adhesions

Hepatic Abscess Usually there is adequate clinical support and the serologic findings are normal Analysis of the stools may reveal *Endamoeba histolytica*

Malignant Growth The outline of the tumor is not sharply defined or regular in contour Jaundice may be present A primary neoplasm may be discovered in the stomach or elsewhere Serologic findings are normal

Portal Cirrhosis This can usually be diagnosed clinically and, from the laboratory standpoint, without difficulty Jaundice occurs in 35 per cent of cases The spleen is enlarged in 80 per cent of cases Hematemesis occurs in 25 per cent of all cases of cirrhosis and is an early symptom Serologic tests give negative results

17 Claessen, G The Roentgen Diagnosis of Echinococcus Tumors, *Acta radiol*, supp 6, 1928

18 Anderson, C C Difficulties and Fallacies in the Radiological Diagnosis of Hydatid Infection, *J Coll Surgeons, Australasia* 2 301 (March) 1930

Syphilis In cases of hereditary syphilis there are the well known signs of the disease In cases of acquired syphilis the Wassermann reaction is positive, and the irregularities on the anterior surface of the liver due to gummas rapidly disappear under antisyphilitic therapy



Fig 1—*A*, roentgenogram of an infected cyst of the right lobe of the liver with calcification of the pericyst *B*, a large cyst extending from the antero-inferior surface of the liver, showing calcification of its capsule *C*, a large cyst occupying the right lobe of the liver, with marked elevation of the diaphragm and irregular segmentation of its contour *D*, a cyst involving the right lobe of the liver, with marked elevation of the diaphragm Note the increased density of the perihilar basal shadows on the right side, which are described by Anderson as probably representing changes in the lymphatic radicles

The intradermal test may or may not give positive results and is occasionally unreliable, according to Fairley, Fairley and Williams¹⁹

Diaphragmatic Adhesions These usually present an irregular breaking up of the dome of the diaphragm, due to "peaking" or "tenting," and questioning may reveal an old history of basal pleurisy or pneumonia. Serologic tests give negative results.

Surgical Treatment—The surgical treatment of hepatic cysts is not within the purview of this short paper, and for this the reader is referred to the subject as outlined by Harold Dew.

LUNG

Hydatid disease of the lung occurs in 12.5 per cent of cases. In the lung the cyst may be either primary or secondary. The primary cyst

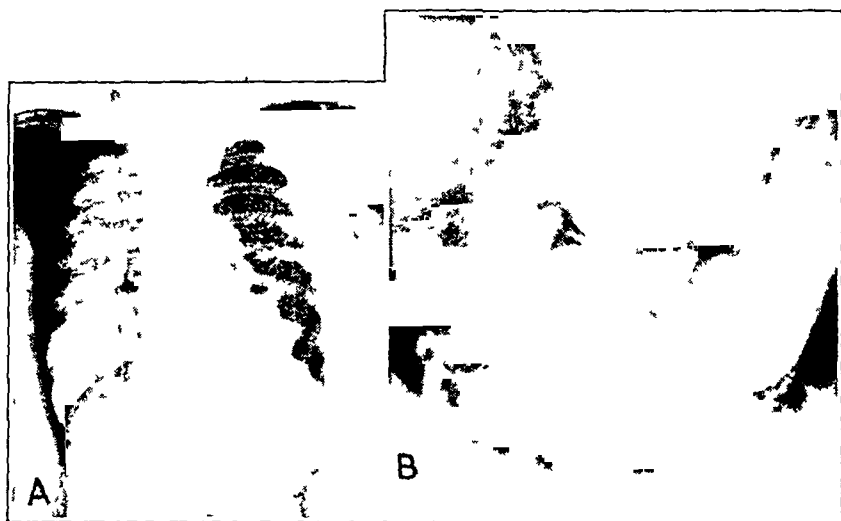


Fig 2—A, calcification of the adventitia of two collapsed cysts involving both the right and the left lobe of the liver. B, a large cyst involving the left lobe of the liver and extending from its lower surface. Note the calcification in the pericyst and its close relation to the lesser curvature of the stomach. Also note the size of the cyst.

is derived from a hexacanth embryo and is carried to the lung. This type is the more frequent. The secondary type develops from blood capsules or scolices.

In cases of pulmonary cysts the distribution is roughly 65 per cent in the right lung and 35 per cent in the left lung, with a special predilection for the base of the right lung. In the lung the adventitia is relatively thin, consequently these cysts rarely become old. As they expand a

¹⁹ Fairley, Keith D., Fairley, N. Hamilton, and Williams, F. Eleanor. Some Fallacies in the Intra-Dermal Test for Hydatid Disease, *M. J. Australia* 2:320 (Sept. 7) 1929.

small bronchus may become included in the pericystic coat and may become occluded. However, the bronchial epithelium is more resistant to fibrosis, and later the patent bronchus may open into the cystic cavity, permitting extravasation of the germinal membrane and brood capsules, as well as the grapelike daughter cysts which are sometimes present and which may be coughed up. Expansion of the cyst usually is more marked toward the pleural surface of the lung, so that in time these cysts frequently lie just beneath the pleura. In some cases the diagnosis is rendered difficult because of the presence of free pleural fluid, and it may be necessary for the pleurisy to resolve before the condition can be diagnosed.

When a pulmonary cyst breaks down it may rupture into a bronchus or, particularly if it lies in a subpleural position, it may rupture into the pleural space. When it ruptures into a bronchus there is usually a rush of salty-tasting clear fluid into the mouth, and if the cyst contains daughter cysts, the patient coughs up "something that looks like grape skins."

When deeply placed parabronchial cysts rupture, the possibility of spontaneous recovery is good. Lepicard²⁰ and Bellard²¹ have stated that in from 80 to 90 per cent of these cases natural cure results.

In cases of subpleural cysts the chances of spontaneous cure are not so promising, and early surgical treatment is required either before or after rupture. The typical cyst is slightly ovoid or elliptic, though it may be circular.

The more frequent location of the pulmonary cyst is in a subpleural position. If it is flattened on one side it is usually at the place of contact with the wall of the chest or with the diaphragm and liver. The adventitial layer of the wall of these cysts is frequently thin as they rarely become old, hence the only roentgenographic finding may be a cystic area filled with fluid. If only one cyst exists, it is more frequently found posteriorly at the base of one lung, whereas if several cysts are present, according to Anderson,²² the greater portion of one or both lungs may be displaced.

When the cyst communicates with a bronchus, the foul sputum may simulate that of bronchiectasis. Brailsford²³ suggested that iodized poppy-seed oil 40 per cent be used to demonstrate these cavities.

²⁰ Lepicard, S. La vomique hydatique pulmonaire, These de Paris, no 290, 1912.

²¹ Bellard, L. Contribution a l'etude de la vomique, hydatique curative. These de Paris, no 105, 1924.

²² Anderson, C. C. Radiological Diagnosis of Hydatid Infection, Brit J Radiol 1 428 (Nov) 1928.

²³ Brailsford, James F. Hydatid Disease in England. Brit M J 1 133 (Jan 24) 1931.

Kohler,²⁴ in discussing large circular shadows in the lung, stated that they may be produced by echinococcosis, carcinoma, sarcoma, abscess, interlobar empyema, actinomycosis, infarct and intrathoracic struma. It is well to include dermoid cysts in this list. These conditions will now be briefly considered separately.

Differential Diagnosis—**Carcinoma** Carcinomatous tumors are usually multiple, the growth is more rapid than that of a hydatid cyst and the outline of the metastases is not so sharply defined as that of a hydatid cyst. Usually it is possible to demonstrate a primary growth, and there is considerable cachexia. No eosinophilia is present. Serologic examination reveals no abnormality.



Fig 3—A case of apparently spontaneous cure. The patient, a man aged 55, stated that ten years previously he coughed up “about 500 grape skins” and was in poor health. He now is in excellent health and weighs 45 pounds (20.5 Kg) more than he did ten years ago. A Casoni test was recently performed and gave a negative result. At present there is little excursion of the left dome of the diaphragm, and much fibrosis is present at the base of the left lung.

Sarcoma A primary growth may be demonstrable, and cachexia may be present. Bull²⁵ stated that the edges fade into the surrounding pulmonary tissues, giving much the same picture as seen in the earliest stages of pulmonary abscess. However, some round, “cannon-ball” sarcomatous deposits are sharply defined at the periphery and show a

²⁴ Kohler, A. *Röntgenology*, ed 2, London, Baillière, Tindall & Cox, 1935, p 385.

²⁵ Bull, H. Cecil H. *X-Ray Interpretation* London, Oxford University Press, 1935, p 316.

greater density than a hydatid cyst. No eosinophilia is present. Serologic examination reveals no abnormality.

Abscess. Abscess may follow tonsillectomy or infection from a known focus. There is a septic type of temperature curve. No eosinophilia is noted. Serologic tests give negative results.



Fig 4—*A*, a large cyst filled with fluid, occupying the midportion of the right lung. There is also considerable elevation of the right dome of the diaphragm, owing to the presence of a cyst in the right lobe of the liver. *B*, an oblique view of the same patient as shown in *A*. Note the anterior position of the cyst in the lung and the density of the cyst as compared with the shadow caused by the heart. The loss of definition of the cysts speaks for infection and inflammatory changes. *C*, a cyst occupying the midportion of the left lung. Note its flattened lateral surface. *D*, a lateral view of the same patient as shown in *C*.

Interlobar Empyema Frequently interlobar empyema follows pneumonic consolidation. There is a septic type of temperature curve, and other findings are similar to those noted in cases of pulmonary abscess.

Actinomycosis Actinomycosis is due to the *Streptothrix* organism. Pleural adhesion usually develops, but occasionally empyema results. This disease spreads by contiguity through all the tissues. When a subcutaneous abscess ruptures or opens, granules of sulfur may be found. The clinical findings are similar to those in pulmonary tuberculosis. Serologic tests give negative results.

Infarct After the formation of a thrombus in the heart, which may be associated with coronary occlusion, an infarct may develop. No eosinophilia is noted, and serologic tests give negative results.

Intrathoracic Struma Frequently intrathoracic struma is associated with dysphagia and dyspnea, rarely is cardiac embarrassment noted. There may be hyperthyroidism. No eosinophilia is present. Serologic tests give negative results.

Dermoid Cysts Dermoid cysts are easily distinguishable roentgenographically because of the contents, such as teeth or ossicles. Growth is very slow. Sometimes a dermoid cyst shows a changing fluid level when the patient alters his position.²⁶

KIDNEY

Hydatid disease of the kidney is rare (2.3 per cent, Dédé), because of the difficulty for the hexacanth embryo to pass through both the hepatic and the pulmonary filter. When it does occur it may involve either the perirenal or the parenchymal tissue, in the latter case causing pressure atrophy of the renal substance. In the majority of cases the cyst ruptures into the renal pelvis and drainage results, but eventually stagnation of the urine occurs, disposing toward pyelitis and pyelonephritis. Occasionally, previous to rupture the cyst may encroach on the ureter or on one of the major calices, resulting in hydronephrosis. At times, after the breakdown of the cyst, the cystic wall or other hydatid elements become impacted in the ureter. This is followed by renal pain and colic. The pain may be intermittent or persistent and has been known to last for years. During these attacks, hematuria may be present, and the urine may contain hydatid membrane, scolices, daughter cysts or hydatid fluid.

²⁶ Phemister, Dallas B., Stenn, William B., and Volderaner, John C. A Roentgenologic Criterion of Dermoid Cyst, *Am J Roentgenol* **36** 14 (July) 1936.

Dew⁶ has listed the following indications for nephrectomy

- 1 Conversion of the whole organ into a cystic mass, the kidney appearing as a mere appendage to the cyst
- 2 Multiple cysts of the kidney, when conservative measures would be difficult or impossible
- 3 Complications, such as existent calculi, pyonephrosis or infection confined to the kidney
- 4 Fistulous communications with the intestines
- 5 Complications during operation, such as hemorrhage or contamination of the area

Cysts of the kidney have no distinctive roentgenographic appearance. A barium sulfate enema may aid in localizing the cyst. The serologic tests give positive results. The finding of a hydatid membrane, scolices or hooklets in the urine makes the diagnosis positive.

Differential Diagnosis—Hypernephroma. Hypernephroma is characterized by an insidious development, hematuria, no eosinophilia and negative results of serologic tests.

Paravertebral Abscess. Paravertebral abscess is associated with Pott's disease of the spine.

SPLEEN

The spleen is involved in about 2 per cent of cases. The cyst is usually primary, in that the hexacanth embryo is carried to it by way of the blood stream. A cyst of the spleen is usually single and may reach enormous proportions. In a case recorded by Wilson²⁷ the cyst reached into the bony pelvis. Pain is usually dull, and frequently there is a feeling of heaviness in the upper portion of the abdomen. At times there are nausea and vomiting. Clinically there may be bulging of the ribs, as well as an epigastric mass below the left costal margin. As stated previously on rupture of a splenic cyst, hydatidosis frequently results. In cases in which the cysts are multiple, a cardiac origin should be suspected.

The treatment advocated is splenectomy, since it offers a possibility of complete removal of the parasite and causes only passing changes in the nature of the elements of the blood.

Roentgenographically the barium meal may reveal distortion of the greater curvature of the stomach, and a pyelogram may assist in differentiating renal conditions.

Differential Diagnosis—This includes a consideration of the Grawitz tumor and hydronephrosis. These can easily be eliminated by laboratory methods.

²⁷ Wilson, T. G. A Case of Hydatid Cyst in the Spleen Simulating an Ovarian Cyst, *J. Obst. & Gynaec. Brit. Emp.* 7:413, 1905.

BONE

The diagnosis of hydatid infection of the bone is difficult. This condition occurs in only 0.9 per cent of cases of hydatid infection, according to Deve. A peculiarity of this condition is that there is no adventitia. In fact, the fibrous tissue usually laid down by the host is absent, and the outer surface of the cyst contains numerous osteoclasts. In the long bones the most helpful diagnostic finding is a burrowing multilocular growth which invades and destroys the bone and leaves a chain of "punched-out appearing areas" of decreased density. Periosteal reaction is lacking until the cortex is broken through.



Fig. 5—A large partially calcified cyst occupies the upper pole of the enlarged spleen. Note its relation to the upper part of the stomach.

At other times the multilocular appearance of the area involved closely simulates that of a giant cell tumor. The organism extends along the haversian canals, and occlusion of the small arteries occurs. This permits necrosis of the bone, with the occasional formation of cavities containing hydatid cysts.

If the periosteum is involved, it reacts only feebly and is violated early. After reaching the soft tissues, the parasite shows the typical univesicular type of growth, with the formation of a fibrous adventitia. The end of hydatid disease of all long bones is pathologic fracture, which practically never heals. The serious import of this condition in bone makes complete excision of the infected area imperative. Incision, curettage and treatment with formaldehyde are unsatisfactory. A bone

graft should be inserted after the diseased bone has been removed. In cases in which the soft tissues also have been involved, amputation above the area involved is the method of choice. Roentgen treatment has not proved satisfactory, according to Deve, Billiard and Decoulare-Delafontaine²⁸

Involvement of various flat bones has been recorded, the ilium being most frequently affected. This condition is characterized by slowly growing, painless, fluctuant, nodular swelling. Limitation of movement follows involvement of the acetabulum. Late in the condition there may be irritation of the lumbosacral nerves.

In flat bones the roentgenogram shows closely packed cystic involvement of the bone, the cysts are separated by coarse trabeculae, and the cancellous structure of the bone is distorted, appearing burrowed and expanded. The cortex may be irregularly thickened, owing to osteoblastic reaction, and a multilocular appearance may result. Small islands of calcium may be seen scattered throughout the diseased cystic area.

Differential Diagnosis—Hydatid disease of bone must be differentiated from carcinomatous and sarcomatous deposits, enchondroma and endosteal sarcoma, as well as fibrocystic disease and myeloma.

The entire absence of actual bony reaction is helpful in diagnosing hydatid disease. Hydatid cysts of bone are usually unrecognized until late.

Brailsford²⁹ described a case of hydatid disease of the mediastinum in which treatment for tuberculous abscess was given in a sanatorium. Eventually the vertebrae were involved.

BRAIN

Involvement of the brain occurs in 0.6 per cent of cases and may be either primary or secondary. The primary form, as in the case of the kidney, is derived from a hexacanth embryo and is carried by the blood stream. This type is more frequently found in children. The cysts are usually single. The secondary form is derived from hydatid elements and is frequently multiple. It is usually found in adults. Manifestations of the two types are quite different.

Primary cysts are at least seven times as frequently found in children less than 15 years of age as in adults. Owing to the impossibility of expansion, hydatid cysts of the brain give rise to serious symptoms before they have assumed large proportions. Therefore, children suffering from this condition usually do not reach adult life.

28 Deve, F., Billiard, A., and Decoulare-Delafontaine, A. Sable hydatique et radiothérapie pénétrante, *Compt rend Soc de biol* **91** 1365 (Dec 20) 1924.

29 Brailsford, J. F. Diseases of the Hip-Joint and Its Immediate Neighbourhood, *Brit M J* **1** 92 (Jan 16) 1932.

In the primary type of involvement there is increased intracranial pressure, usually associated with increased pressure of the cerebrospinal fluid. Owing to this increased intracranial pressure, molding and thinning of the bones of the skull and osteoporosis may occur. According to Dew,³⁰ this may be so pronounced that palpation over the area may



Fig 6—*A*, hydatid disease involving the upper fourth of the tibia. Note the expansion of the cortex, the displacement of the fibula and the resemblance to giant cell tumor. *B*, hydatid disease of the crest and body of the ilium. Note the appearance of burrowing, with irregular cavitation and destruction of the architecture of the bone. Also note the ankylosis of the hip joint following involvement of the acetabulum. *C*, a similar type of case to that shown in *B*. Again note the ankylosis of the hip joint.

elicit crackling or pressure may cause indentation. Headache is common, and there may be jacksonian epileptiform seizures, which are sometimes followed by paralysis.

³⁰ Dew,⁶ p. 359

Differential Diagnosis—This is difficult, since different neoplastic conditions give rise to confusing neurologic symptoms. Aspiration of the cystic contents is perilous. If the cyst is primary, operation should be performed as soon as possible. If multiple cysts are present, the condition is hopeless, and death from pressure is usually not long delayed.

PERITONEUM AND PELVIS

Involvement of the peritoneum or pelvis usually comes about in one of two ways, first, by extrusion of an intact simple cyst from the liver or spleen and, second, by rupture of a cyst in the liver or spleen, with spilling of the hydatid elements over the peritoneal surfaces.

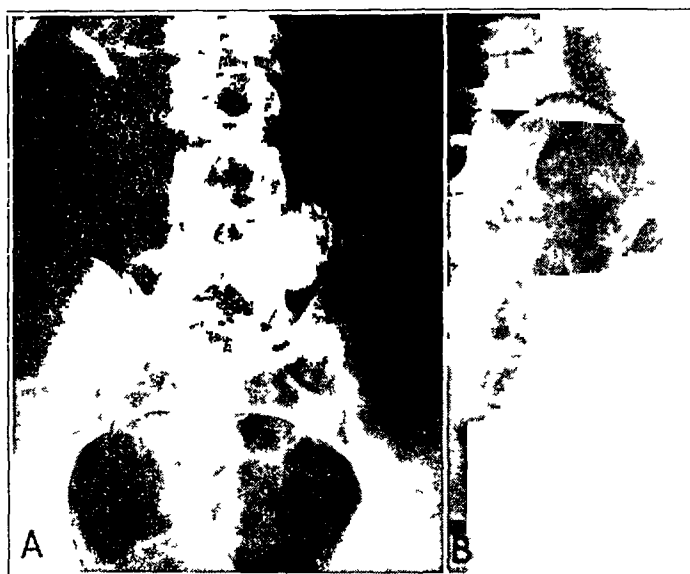


Fig 7—*A*, one large and several small hydatid cysts attached to the omentum. *B*, a large omental cyst situated just below and pressing on the dye-filled gallbladder.

Dew³¹ called the latter catastrophe hydatidosis, it represents the sowing and survival of numerous hydatid elements. In the female the elements are prone to lodge in the pouch of Douglas. Either a vaginal or a rectal examination will aid in the diagnosis when the condition is suspected.

Obviously it is difficult to diagnose a cyst in the abdomen or pelvis, except when there are calcareous changes in the adventitia. Over 90 per cent of these cysts are secondary, and a history suggestive of rupture of a primary cyst at some time in the past may be obtained. After an injury a patient may give a history of various degrees of anaphylaxis, urticaria or erythema.

³¹ Dew⁶ p 106

Clinically a chessboard arrangement of alternating areas of dulness and resonance may reveal the true condition. This sign is not found in any other condition.

HEART, MUSCLES AND OTHER TISSUES

The heart, muscles and other tissues are rarely involved, and the findings will not be discussed in this paper. However, a roentgenogram made in one interesting case will be included (fig 8).

LOCALIZATION

After discovering that a cyst is present, the roentgenologist should seek to localize it. This may be done by using films taken with the patient

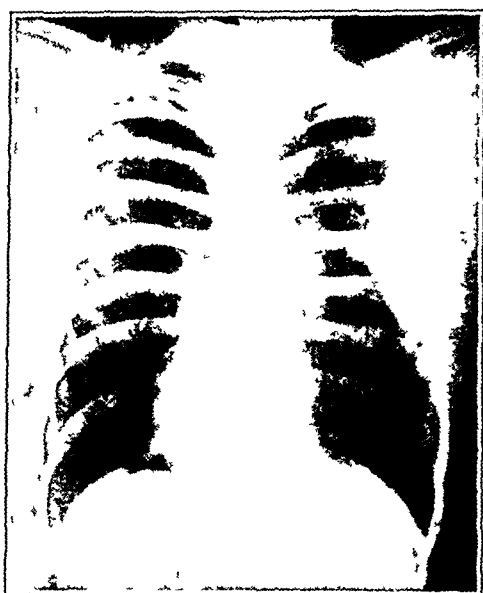


Fig 8—A hydatid cyst located in the posterior axillary region and entirely confined to the soft tissue.

in the anteroposterior and in the lateral position or by using stereoscopic films of the chest or abdomen. The best means of localization yet devised is that of Johnson³² by means of stereoroentgenometry. By this method it is possible to measure accurately the size of the cyst and to determine its position.

Another method recently described involves use of the tomograph, devised by Chaoul,³³ of Berlin. By taking anteroposterior serial roentgenograms through the chest or abdomen in various successive parallel planes it is possible to demonstrate the cyst, its contents and its position accurately.

32 Johnson, Clayton R. Roentgen Mensuration by Stereoroentgenometry, *Radiology* 25 492 (Oct) 1935.

33 Chaoul, R. Personal communication to the author.

Pneumoperitoneum—A few years ago pneumoperitoneum was strongly advocated by Uspensky³⁴ and others. However, it has failed to be of great diagnostic moment and is not without risk, particularly when infected cysts may be present.

NEEDLING

Promiscuous needling is to be condemned. After this procedure unfortunate sequelae have been recorded, such as introduction of sepsis, contamination of surrounding healthy tissues, puncture of a blood vessel, followed by hemorrhage, rupture of a pulmonary cyst into a bronchus, resulting in anaphylactic shock which sometimes causes death, and death due to drowning.

SURGICAL TREATMENT

Fortunately the anaphylactic state is abolished under general anesthesia, so that serious symptoms are not forthcoming when toxic material is spilled into the wound. However, at times there may be a delayed reaction due to slow absorption of cystic fluid following surgical treatment. Hence it is well for the surgical field to be well protected by packs made of black gauze so that absorption of hydatid elements can be visualized if spilled and absorption of the fluid avoided.

SUMMARY

The history and distribution of hydatid disease and the life cycle of *Taenia echinococcus* are considered.

The incidence of hydatid disease of various organs is discussed, and it is shown that the liver is the most frequent site of infection in human beings.

The diagnosis and laboratory tests, including the precipitin, the Casoni and the complement fixation test, are considered.

The roentgenographic findings in the organs and tissues principally involved, together with a brief differential diagnosis, are given.

NOTE—References cited in footnotes 5, 6, 14, 20, 24 and 25 were included on the authority of other writers.

Dr. Edwards and Professor Harold Dew rendered valuable assistance in the preparation of this article.

³⁴ Uspensky, A. E. Diagnostic Importance of Pneumoperitoneum, *Brit. J. Radiol.* **32**: 14 (April) 1927.

THE ADRENALS AND EXPERIMENTAL PANCREATIC DIABETES

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The etiology and course of diabetes mellitus have been associated with adenal function by various authors since Zuelzer¹ proposed the view that a mutual antagonism exists between the adrenals and the pancreas. He said he believed that the glycosuria which follows pancreatectomy is due to the unchecked diabetogenic action of epinephrine secreted from the adrenals in the absence of the antagonistic action of internal secretion of the pancreas.

More recently the supposed relationship of the adrenals to diabetes and to other diseases has become the basis for surgical intervention or roentgen irradiation of the adrenals in clinical practice. In view of the fact that these procedures involve possible irreparable damage to the indispensable adrenal cortex as well as to the less essential medulla, they should be based on physiologic premises that have indisputable experimental support, or else they should be condemned as too dangerous for life and health to warrant their use as therapeutic measures. We believe that the experimental background for the alleged relation of the adrenals to diabetes is inadequate. One of us² has already emphasized the possible serious consequences of surgical intervention on the adrenal glands and has reported the development of Addison's disease following an operation on a patient with diabetes.

Some writers have maintained that the medulla is concerned with diabetes, others believe that it is the cortex. Some apparently have

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Eli Lilly & Co. supplied the insulin for this and related investigations.

A preliminary report of this work has been published (*Proc Soc Exper Biol & Med* **34** 100 1936).

Aided by the G N Stewart Memorial Fund and grants from the Commodore Beaumont Foundation and Mr Max Manischewitz.

1 Zuelzer, G. (a) *Experimentelle Untersuchungen uber den Diabetes*, *Berl klin Wchnschr* **44** 474, 1907, (b) *Ueber Versuche einer spezifischen Fermenttherapie des Diabetes*, *Ztschr f exper Path u Therap* **5** 307, 1908.

2 Rogoff, J M. Addison's Disease Following Adrenal Denervation in a Case of Diabetes Mellitus, *J A M A* **106** 279 (Jan 25) 1936.

considered the adrenal as a single gland, failing to note functional distinction between the indispensable interrenal glandular tissue, or cortex, and the chromaffin material, or medulla, of the adrenal body. An extensive literature has accumulated on the alleged rôle of the adrenals in carbohydrate metabolism, much of which fails to indicate whether the supposed influence of the glands is exercised by the cortex or the medulla or both.

Possible relationship of the adrenal medulla to diabetes can be studied more easily than that of the adrenal cortex. The output of epinephrine can be measured, and the rate of secretion of epinephrine in normal animals under ordinary experimental conditions is known.

Liberation of epinephrine can be suppressed without serious consequences in otherwise normal animals.⁴ If secretion of epinephrine plays a significant rôle in experimental pancreatic diabetes, its suppression should affect the development or course of diabetes in depancreatized animals. We have made experimental studies to determine whether this occurs and also quantitative as well as qualitative studies of secretion of epinephrine in relation to experimental pancreatic diabetes.

In previous communications⁵ it was reported that unilateral adrenalectomy or interference with secretion of epinephrine (by adrenal denervation and other procedures) ameliorated diabetes in depancreatized dogs, that in animals previously rendered diabetic (by pancreatectomy) the adrenal operation diminished the glycosuria and that in dogs previously subjected to the adrenal operation pancreatectomy failed to cause or caused only a mild degree of glycosuria. The amount of insulin required (on a constant diet) for controlling the glycosuria was reported to be decidedly less as the result of the adrenal operations, which were said also to render the animals more sensitive to insulin. These statements are in agreement with conclusions reported by others.

3 Stewart, G. N., and Rogoff, J. M. The Average Epinephrin Output in Cats and Dogs, *Am J Physiol* **66** 235, 1923.

4 Stewart, G. N., and Rogoff, J. M. (a) Quantitative Experiments on the Liberation of Epinephrin from the Adrenals After Section of Their Nerves, with Special Reference to the Question Whether Epinephrine Is Indispensable for the Organism, *J Pharmacol & Exper Therap* **10** 1, 1917, (b) Further Observations Showing that Epinephrine from the Adrenals Is not Indispensable, *Am J Physiol* **48** 397, 1919.

5 (a) Barnes, B. O., Scott, V. B., Ferrill, H. Ward, and Rogoff, J. M. Effects of Partial Adrenalectomy on Experimental Diabetes and on Sensitivity to Insulin, *Proc Soc Exper Biol & Med* **31** 524, 1934, (b) The Effects of Partial and Complete Adrenalectomy on Experimental Diabetes, *Am J Physiol* **109** 35, 1934, Further Studies on the Effects of Partial Adrenalectomy on Experimental Diabetes, *ibid* **109** 89, 1934, The Sensitivity to Insulin, *ibid* **109** 95, 1934 (c) Ferrill, H. Ward, Rogoff, J. M., and Barnes, B. O. Further Studies on the Influence of the Adrenal Glands on Experimental Diabetes, *ibid* **113** 41, 1935.

On further examination of the experimental data and in view of satisfactory control experiments, we found it necessary to revise the foregoing interpretations. Under more suitable conditions, we have repeated the experiments and have made more extensive quantitative studies of the output of epinephrine from the adrenals of experimental animals and of an adequate series of control depancreatized dogs. In the former series of experiments the adrenal operations were performed by one of us (J. M. R. assisted by E. N. N.) and the pancreatectomies by another collaborator (B. O. B. who was assisted by H. W. F.). The postoperative and other experimental conditions were not as satisfactorily controlled as in the present series of experiments. One of the animals (on the history of which was based the statement that little or no diabetes follows pancreatectomy if the adrenals are interfered with) was found at autopsy to possess a substantial portion of pancreas and in one or two others a number of nodes were observed along the duodenum and were preserved for histologic examination. With improved conditions of experimental procedure and suitable controls it became obvious that we had been misled in the evaluation of the previous experimental data.

The present report is concerned chiefly with experiments to determine whether reduction or suppression of secretion of epinephrine from the adrenal glands exerts a significant influence on experimental pancreatic diabetes.

In these, as in the earlier experiments, the criterion was the amount of insulin required to maintain the level of sugar excreted in the urine below about 5 Gm daily and the concentration of sugar in the urine under about 1 per cent. The experiments were performed on dogs. All the experimental and control animals were kept under identical or comparable conditions and on a constant diet, consisting of 500 Gm of boiled beef lung and 100 Gm of sucrose daily, divided into two meals. To the morning meal was added 50 Gm of fresh raw beef pancreas. Drinking water was available at all times. The amount of insulin for each day was divided into two doses and given at the time of feeding. Urine was collected for twenty-four hours, the quantity excreted and the sugar content were determined at the same hour each morning.

Interference with secretion of epinephrine was accomplished by excision of one adrenal gland and denervation of the other gland. In addition to denervation, the medulla of the remaining gland was curetted by drilling with a dental burr so that most of the medulla was destroyed or damaged. For these animals the adrenal operations were performed in two stages, and pancreatectomy was performed during the interval between the adrenal operations. Other dogs were depancreatized without the subsection of the adrenals to operations for reducing the secretion of epinephrine. These served as controls. All the surgical operations in this series were performed by one of us (J. M. R., assisted by E. N. N.). A number of additional experiments were carried out in which the surgical procedures were performed by the other of us (H. W. F.). At the end of different periods of observation the experiments were terminated, so that quantitative determination of the degree of reduction or suppression of secretion of epinephrine could be made (by the method employed by Stewart and Rogoff).

Twenty-one animals were studied in this series of experiments. In these, as well as in some of the better experiments of the previous group, after a few weeks of observation the animals usually showed a reduction in the amount of insulin required to maintain glycosuria at the low level. This cannot be attributed to loss of weight, since the animals of the present series lost little if any weight, although most of the former animals were in much poorer condition. It might appear that in depancreatized animals subjected to interference with secretion of epinephrine from the adrenals the reduced requirement for insulin is due to reduced secretion of epinephrine. However, this cannot be the case, since the requirement for insulin does not decline until several weeks after pancreatic diabetes has been induced. Indeed, it appears at a time when regeneration of nerves might occur in the animals after adrenal denervation and when secretion of epinephrine might be expected to have become reestablished. In any case, the reduction of the amount of insulin required cannot be attributed to the operation for suppression of secretion of epinephrine, since it occurs in control depancreatized dogs not subjected to adrenal operations but otherwise under the same conditions as the experimental animals.

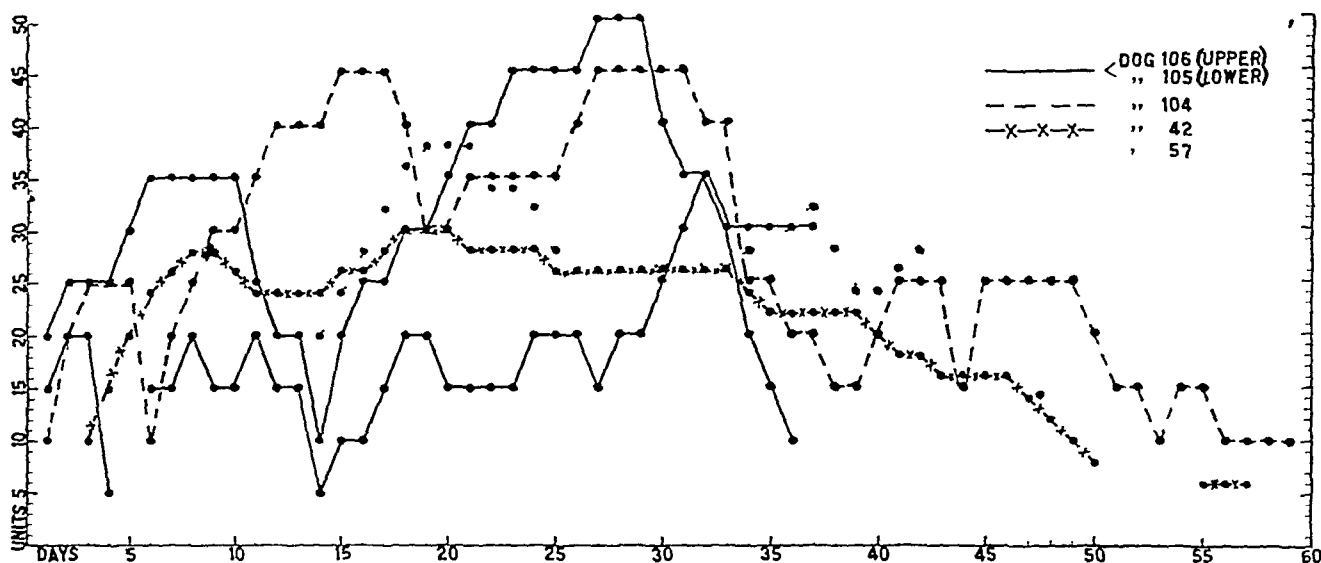
We have observed the decline in requirement for insulin in experimental animals with reduced or suppressed secretion of epinephrine and in some with the ordinary normal rate of secretion (indicating either inadequate denervation or regeneration of adrenal nerves). It is obvious that the requirement for insulin is not modified by the functional state of the adrenal medulla. The range of dosage of insulin required over a period of weeks or months is similar in control depancreatized dogs and in those with a reduced or suppressed output of epinephrine. We have found a high or low requirement for insulin associated with a low or normal output of epinephrine. This may be seen in different animals or in one animal at different times, regardless of whether or not, in addition to pancreatectomy, secretion of epinephrine has been suppressed.

The most significant observation that we have made is that in control depancreatized dogs (not subjected to interference with the adrenals), kept under the same conditions as the other experimental animals, sooner or later the output of epinephrine from the adrenals may become markedly reduced or suppressed. This phenomenon and the possible mechanism responsible for it are still under investigation and will be the subject of another report.

The accompanying chart illustrates the general results obtained. One record (dog 42), the best for the former experiments, is included because the interval between the adrenal operations and pancreatectomy was much longer than that in the later experiments, the rest are for the present series. Each record represents a typical experiment, illus-

trating the various results obtained for different groups of the series. Two dogs (42 and 57) were subjected to operations for suppression of secretion of epinephrine in addition to pancreatectomy, the other three were only depancreatized. These five experiments will be described in the following condensed protocols.

Dog 42—Both adrenals of this female dog were denervated, and the medulla was drilled, the left on July 13 and the right on July 21, 1934. On Jan 2, 1935, pancreatectomy was performed. During the ensuing five weeks the requirement for insulin ranged between 24 and 30 units daily, then it declined during the next three weeks to 6 units daily. On March 1 (fifty-eight days after pancreatectomy) the animal (weight, 6.05 Kg) was killed and the output of epinephrine from the adrenals was determined. With the animal under pentobarbital anesthesia blood was obtained from the adrenal vein by way of the "cava pocket." The rate of blood flow during collection was 1.53 Gm per minute. The concentration of



The requirement for insulin, with a daily diet of 500 Gm of boiled beef lung, 100 Gm of cane sugar and 50 Gm of raw beef pancreas, after pancreatectomy with and without suppression of secretion of epinephrine from the adrenal glands of dogs

epinephrine was estimated, a segment of rabbit intestine being used. The epinephrine concentration in the blood from the adrenal vein was much less than $1/30,000,000$ and somewhat less than $1/50,000,000$, which was the limit of sensitivity for the segment. If the blood from the adrenal vein contained this concentration, it would correspond to 0.00003 mg per minute for the dog or 0.000005 mg per kilogram per minute, i. e., about one fiftieth of the average output for normal animals, as determined by Stewart and Rogoff³ (1923). There probably was not more than one seventy fifth to one one hundredth of the average output of epinephrine for normal dogs under ordinary experimental conditions.

Dog 57—On April 6, 1935, the right adrenal was removed from this male dog (weight 13.5 Kg). On April 26 pancreatectomy was performed, the animal weighing 13.7 Kg. On May 9, when the weight was 11.6 Kg, the left adrenal was denervated, and the medulla was drilled. From April 30 to May 3, inclusive, the

dosage of insulin was doubled by mistake (insulin containing 40 units instead of 20 per cubic centimeter being used), reaching 70 or 80 units daily, without ill effect. Thereafter, the requirement for insulin ranged between 24 and 38 units daily. On June 8, forty-three days after pancreatectomy (weight, 11.2 Kg), the requirement for insulin was 28 units (ascending), and the sugar content of the blood (a m) was 320 mg per hundred cubic centimeters. The animal was used for epinephrine assay. With the animal under pentobarbital anesthesia, blood was obtained from the adrenal vein by way of the "cava pocket." The rate of blood flow during collection was 27 Gm per minute. The remaining adrenal gland (left) weighed 0.57 Gm, it had undergone fibrosis, and the upper half was sclerotic. The concentration of epinephrine in the blood from the adrenal vein was much less than 1:50,000,000 and not as great as 1:75,000,000. If the blood contained 1:75,000,000 epinephrine, the output would correspond to 0.000035 mg per minute for the dog, or 0.0000031 mg per kilogram per minute, i. e., the output of epinephrine was less than one seventy-fifth of the average output for normal animals under ordinary experimental conditions.

Dog 104—Pancreatectomy was performed on this female dog (weight, 8.8 Kg) on Sept. 26, 1935. The requirement for insulin for about a month ranged between 25 and 40 units daily, then it fell, ranging between 15 and 25 units daily for about three weeks. On November 25 (sixty days after pancreatectomy), when the dog weighed 7.65 Kg, the insulin requirement was 10 units daily. The animal was used for epinephrine assay. With the animal under pentobarbital anesthesia, blood was obtained from the adrenal vein by way of the "cava pocket." The rate of blood flow during collection was 8.67 Gm per minute. The left adrenal gland weighed 0.64 Gm and the right gland 0.70 Gm. Epinephrine concentration in the blood from the adrenal vein was distinctly less than 1:125,000,000, somewhat less than 1:250,000,000 and slightly greater than 1:375,000,000. It was taken at 1:300,000,000, corresponding to an output of 0.0000286 mg per minute for the dog, or 0.0000037 mg per kilogram per minute, i. e., about one seventieth of the average output of epinephrine for normal dogs under ordinary experimental conditions.

Dog 105—Pancreatectomy was performed on this male dog (weight, 8.5 Kg) on Oct. 26, 1935. The requirement for insulin during most of the entire period of observation ranged between 15 and 20 units daily. On Dec. 2 (thirty-seven days after pancreatectomy) when the dog weighed 7.4 Kg and the requirement for insulin was 10 units, it was used for epinephrine assay. With the animal under pentobarbital anesthesia blood was obtained from the adrenal vein by way of the "cava pocket." The rate of blood flow during collection was 4.95 Gm per minute. The left adrenal gland weighed 0.47 Gm and the right one 0.5 Gm. Epinephrine concentration in the blood of the adrenal vein was greater than 1:12,000,000, somewhat greater than 1:6,250,000 and less than 1:3,750,000. The reaction on the segment of intestine was not unlike that of 1:5,000,000. It was taken at 1:5,000,000, corresponding to an output of epinephrine of 0.001 mg per minute for the dog, or 0.000135 mg per kilogram per minute, i. e., within the usual range for normal dogs under ordinary experimental conditions.

Dog 106—Pancreatectomy was performed on this female dog (weight 9.5 Kg) on Oct. 26, 1935. The requirement for insulin rose to 50 units daily during about a month and then declined to 30 units daily for the last five days of observation. On December 3 (thirty-eight days after pancreatectomy), when the animal weighed 8.5 Kg and the requirement for insulin was 30 units daily, it was used for epinephrine assay. With the animal under pentobarbital anesthesia, blood was

obtained from the adrenal vein by way of the "cava pocket" The rate of blood flow during collection was 4.25 Gm per minute The adrenal glands weighed 0.56 Gm each Epinephrine concentration in the blood from the adrenal vein was decidedly greater than 1:5,000,000, somewhat greater than 1:3,750,000, less than 1:2,500,000 and not far from 1:3,125,000 It was taken at 1:3,000,000, corresponding to an output of epinephrine of 0.0014 mg per minute for the dog, or 0.00017 mg per kilogram per minute, i e., within the usual range for normal dogs under ordinary experimental conditions

For three animals (dogs 56, 57 and 60) the dose of insulin was doubled by mistake A supply of insulin containing 40 units per cubic centimeter was used, whereas previously the insulin contained 20 units per cubic centimeter For four days, instead of the intended 35 to 40 units daily, the animals received 70 to 80 units daily before the error was discovered In two instances one adrenal gland had been excised and pancreatectomy performed, in the third case one adrenal gland was denervated before pancreatectomy No ill effects were observed from these enormous doses of insulin We must conclude, therefore, that in depancreatized animals the supposed increase in sensitivity to insulin reported to occur after unilateral adrenalectomy or adrenal denervation is without foundation A number of animals that had only been depancreatized were killed at intervals of about one to eight weeks after removal of the pancreas The output of epinephrine was determined for these to observe how soon reduction might be detected In some the requirement for insulin at the time was relatively high, in others it was low A reduction in the secretion of epinephrine was found as early as ten and eleven days after pancreatectomy in some animals, while in others a normal output of epinephrine was found five or six weeks after pancreatectomy We found no relation between the requirement for insulin and the rate of secretion of epinephrine in the animals studied

COMMENT

The literature on the adrenal glands in relation to carbohydrate metabolism is too extensive for us to attempt more than a review of a few papers that have a more or less direct bearing on the particular phase of the subject under consideration The earlier papers are concerned chiefly with the question of relationship of the adrenal medulla, although some of them do not make clear whether a relationship of the medulla or of the cortex is supposed to exist In the more recent literature can be found support for either view, i e., that the cortex plays an important or indispensable rôle in carbohydrate metabolism or that the medulla plays such a rôle

Studies of the influence of administration of epinephrine on carbohydrate metabolism may be viewed as being mainly of pharmacologic interest Few investigations of this nature can have physiologic sig-

nificance, since the dosage of epinephrine is usually much in excess of the amounts known to be within the physiologic range of secretion. Often the epinephrine is administered subcutaneously. Owing to the local vasoconstrictor action of epinephrine absorption is rarely at a uniform rate, indeed, differences in physiologic action have been reported between the subcutaneous and the intravenous administration of the same quantities of epinephrine.

Of those who have supported the view that the cortex is directly concerned in an important manner with carbohydrate metabolism, none can be said to have produced adequate experimental proof. Britton and Silvette⁶ have maintained that the adrenal cortex exercises a "prepotent function" on carbohydrate metabolism and that in adrenalectomized animals the effect on carbohydrate metabolism "appears to be primarily responsible for death." Rogoff and Stewart⁷ have shown that moderate hypoglycemia occurs in adrenalectomized animals when acute symptoms of cortical insufficiency develop. However, some animals may manifest important symptoms of insufficiency and show no significant decline in the sugar content of the blood. This is true, also, for human beings with Addison's disease. The view held by Britton and Silvette that severe hypoglycemia, "commonly to the convulsive level," occurring in animals "as early as 18 to 48 hours after operation," accounts for death of adrenalectomized animals is not tenable in the light of the experimental work of others. The results indicated that their adrenalectomized animals were not in as good condition as they should have been from eighteen to forty-eight hours after operation.

Hartman and Brownell⁸ reported studies on nine cats and concluded that their results indicated that "cortin is essential for the maintenance of diabetes." Although they administered an extract of adrenal cortex, most of their adrenalectomized animals did not survive as long as untreated adrenalectomized cats usually do.⁹ Of course these were also depancreatized. Nevertheless, the conclusions need not be accepted merely because this additional handicap existed. The experiments would be of value only if the depancreatized and adrenalectomized animals

6 Britton, S. W., and Silvette, H. The Apparent Prepotent Function of the Adrenal Glands, *Am J Physiol* **100** 701, 1932.

7 Rogoff, J. M., and Stewart, G. N. Studies on Adrenal Insufficiency in Dogs. II. Blood Studies in Control Animals Not Subjected to Any Treatment, *Am J Physiol* **78** 711, 1926.

8 Hartman, F. A., and Brownell, K. A. Relation of Adrenals to Diabetes. *Proc Soc Exper Biol & Med* **31** 834, 1934.

9 Rogoff, J. M., and Stewart, G. N. (a) Studies on Adrenal Insufficiency. VIII. The Survival Period of Untreated Adrenalectomized Cats, *Am J Physiol* **88** 162, 1929, (b) Studies on Adrenal Insufficiency. IX. The Influence of Extracts of Adrenal Cortex (Sheep and Cattle) on the Survival Period of Adrenalectomized Dogs and Cats, *ibid* **91** 254, 1929.

were in sufficiently good condition to permit studies that were not complicated by serious postoperative conditions. Indeed the only cat that survived long enough to permit satisfactory studies showed a condition exactly opposite to that mentioned in their conclusion. The animal survived thirty-eight days after bilateral adrenalectomy. "For three weeks or more during this latter period there was no reduction in diabetes but after this time there was marked reduction which large amounts of cortin failed to restore." Adrenal cortex extract prepared by Hartman's salt precipitation method has been proved to be incapable of prolonging life in adrenalectomized animals^{9b}. Since then he has employed extracts of adrenal cortex prepared by a different process. It may be pointed out that since Hartman¹⁰ has maintained that the adrenal cortex produces epinephrine, he could not be certain that any effect attributed to action of his extract might not have been due to presence of epinephrine or related principles.

From the pharmacologic antagonism existing between epinephrine and insulin it seems that the alleged relation of the adrenal medulla to pancreatic diabetes rests on a more substantial basis. However, the evidence afforded by properly controlled experimental work and by adequate quantitative studies does not show such a relationship. Older literature on this question has been reviewed in a number of papers by Stewart and Rogoff¹¹ on carbohydrate metabolism, particularly in the paper entitled "The Adrenals and Pancreatic Diabetes"¹². In that paper it was shown that diabetes develops in depancreatized animals in the absence of secretion of epinephrine to the same degree as in those without interference with the adrenals. After total ablation of the adrenals pancreatic diabetes continues to exist if the postoperative consequences of adrenalectomy are not too severe. If adrenalectomy is followed by a rapid decline of the animal and short survival or if after a period of good postoperative recovery acute insufficiency of adrenal cortex supervenes, the sugar content of the blood may fall to or below the normal level, and glycosuria may become considerably diminished.

10 Hartman, F. A., and Hartman, W. B. The Production of Epinephrin by the Adrenal Cortex, *Am J Physiol* **65** 623, 1923.

11 Stewart, G. N., and Rogoff, J. M. The Alleged Relation of the Epinephrin Secretion of the Adrenals to Certain Experimental Hyperglycemias, *Am J Physiol* **44** 543, 1917, The Relation of the Adrenals to Piqure Hyperglycemia and to the Glycogen Content of the Liver, *ibid* **46** 90, 1918, Further Observations on the Relation of the Adrenals to Certain Experimental Hyperglycemias (Ether and Asphyxia), *ibid* **51** 366, 1920, The Action of Insulin on Adrenalectomized Rabbits, *ibid* **65** 342, 1923.

12 Stewart, G. N., and Rogoff, J. M. The Adrenals and Pancreatic Diabetes, *Am J Physiol* **65** 319, 1923.

Turcatti¹³ concluded that combined pancreatectomy and adrenalectomy interfere with the development or reduce the severity of pancreatic diabetes. This did not occur if, instead of adrenalectomy, the glands were denervated. He admitted that his conclusions cannot be considered categorical, since the animals survived for too short a time. None of his fourteen experimental animals survived beyond forty hours. All succumbed within from eight to forty hours.

Carrasco Formiguera and Puche¹⁴ concluded that denervation of the adrenals does not influence pancreatic diabetes. Their experiments were made on two dogs, in one complete and in the other partial pancreatectomy having been performed. Ciminata¹⁵ has supported the view that diabetes in human beings can be successfully treated by denervation of the adrenal glands. This is based on his experiment performed in 1928 on one dog in which he obtained a rapid decrease in the sugar content of the blood and in glycosuria after bilateral denervation of the adrenals.

Cannon, McIver and Bliss¹⁶ obtained an increase in rate of the denervated heart after administration of insulin, when the sugar content of the blood fell to between 70 and 80 mg per hundred cubic centimeters in cats anesthetized with a compound of chloral and dextrose. This increase in heart rate was interpreted as indicating liberation of epinephrine from the adrenals to counteract the insulin hypoglycemia. The effect was not obtained if the adrenals were excised or denervated. It is now evident that the "denervated" heart is not a reliable indicator for quantitative studies on the secretion of epinephrine from the adrenals. Cannon, Lewis and Britton¹⁷ have shown that the so-called denervated heart (as employed by Cannon, McIver and Bliss) may not be entirely denervated, since they found "evidence for accessory accelerator fibers from the thoracic sympathetic chain." Other evidence from the same laboratory shows that the cardio-acceleration may be obtained by influence of the thyroid and of the liver, as well as of the

13 Turcatti, E. Surrenale et diabete pancreatique, *Compt rend Soc de biol* **102** 466 (Nov 8) 1929

14 Carrasco Formiguera, R, and Puche J. Enervation des surrenales et diabete experimental, *Compt rend Soc de biol* **108** 171 (Oct 12) 1931

15 Ciminata, A. Influence of Division of Nerves of Suprarenals on Diabetes Mellitus, *Klin Wchnschr* **11** 150 (Jan 23) 1932, abstr, *J A M A* **98** 1421 (April 16) 1932

16 Cannon, W B, McIver, M A, and Bliss, S W. Studies on the Conditions of Activity in Endocrine Glands. XIII Sympathetic and Adrenal Mechanism for Mobilizing Sugar in Hypoglycemia, *Am J Physiol* **69** 46, 1924

17 Cannon, W B, Lewis, J T, and Britton, S W. Studies on the Conditions of Activity in Endocrine Glands. XVII A Lasting Preparation of the Denervated Heart for Detecting Internal Secretion, with Evidence for Accessory Accelerator Fibers from the Thoracic Sympathetic Chain, *Am J Physiol* **77** 326 1926

adrenal Finally, the acceleration can be obtained even in the absence of the adrenals or of the influence of the thyroid or liver It has been accounted for by Cannon and his collaborators as due to a sympathomimetic hormone, which they called sympathin The reaction relied on by Cannon, McIver and Bliss therefore could not yield reliable quantitative information on adrenal secretion of epinephrine

Whether or not insulin is capable of influencing secretion of epinephrine has not been satisfactorily determined Statements can be found in the literature indicating that insulin is without effect and others that it may affect secretion of epinephrine in either direction Methods of investigation on which these statements are based are not sufficiently reliable In our own experience, by collecting blood from the adrenal vein by way of the "cava pocket" and utilizing rabbit intestine for determining the concentration of epinephrine in the blood, we have failed thus far to find any significant alteration in the rate of secretion of epinephrine from the adrenals after administration of insulin under the conditions of our experiments This question is still under investigation

We believe that the experiments reported in this paper are adequate to show that the alleged relation between the adrenal medulla and pancreatic diabetes does not exist As in the experiments of others, when we made observations on animals that were in poor condition, we also found milder diabetes This we interpret as indicating that the condition of the animal was too poor to enable it to react by the development of glycosuria of the same intensity as may occur in depancreatized animals in good condition For the animals that withstood the experimental conditions better and were obviously in a much more satisfactory physical state, our experiments clearly showed that pancreatic diabetes is not modified by a reducing or suppressing of secretion of epinephrine from the adrenals On the other hand, we have obtained evidence that the diabetic state, under the conditions of our experiments, may lead to interference with liberation of epinephrine from the adrenals We believe, therefore, that the supposed relation of the adrenal medulla to diabetes as a basis for the clinical practice of intervention with the adrenal glands does not have the support of unequivocal experimental evidence

CONCLUSIONS

The supposed dependence of experimental pancreatic diabetes on secretion of epinephrine from the adrenals is not supported by substantial experimental evidence

Severity of diabetes in depancreatized dogs is not modified by reduction or suppression of secretion of epinephrine from the adrenals

The requirement for insulin, when the diet is constant, is within the same range in depancreatized dogs as in dogs with a reduced or suppressed secretion of epinephrine in addition to pancreatectomy

Depancreatized dogs with a reduced or suppressed secretion of epinephrine are not more sensitive to insulin than ordinary depancreatized dogs

Depancreatized dogs kept for several weeks on a constant diet with adequate amounts of insulin to control glycosuria sooner or later show a reduction or suppression of output of epinephrine from the adrenals

Results obtained for depancreatized animals that have been subjected to operations on the adrenals should be interpreted with caution unless the animals are obviously in excellent physical condition

The clinical practice of intervention with the adrenal glands for the relief of diabetes (or other conditions, except unilateral malignant neoplasm) does not rest on unequivocal experimental premises, and it should be deprecated as too dangerous for life and health

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WEIL'S DISEASE

REPORT OF SEVEN CASES

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Weil's disease has been recognized since Weil described the condition in 1886. Whether or not Weil's four cases were actually cases of spirochetal jaundice is not known, since laboratory confirmation was not possible then. Japanese investigators¹ in 1916 published the results of their study of the disease in their country and established the identity of the causative organism, later named *Leptospira icterohaemorrhagiae*.² Since 1916 cases have been reported from Europe, Asia, Africa, South America and North America and Australia.³ In the United States and Canada thirteen cases have been reported in which the etiologic agent was shown to be *L. icterohaemorrhagiae*.⁴ In these thirteen cases the clinical course did not differ materially from the usual course.⁵ In five cases the diagnosis was not made until autopsy.⁶

Some confusion exists in the diagnosis of Weil's disease, consisting chiefly in the differentiation of the disease from infectious jaundice. Weil's disease is a type of infectious jaundice, but all cases of infectious jaundice are by no means to be considered as cases of Weil's disease. Numerous epidemics of infectious jaundice have been investigated in this country, but in no instance were the investigators able to prove the presence of Weil's disease as a part of the epidemic.⁷ Blumer, in 1923, stated that spirochetes had not been demonstrated in any case of jaundice in the United States. The only case reported in the American literature prior to the publication of Blumer's article was that of an accidentally infected laboratory worker.⁸ Langworthy and Moore have stressed the

From the Medical Service of Fitzsimons General Hospital, Denver

1 Inada, Ido, Hoki, Kaneko and Ito

2 Noguchi, 1918

3 Wadsworth and others, Hubner and Reiter, and Uhlenhuth and Fromme, 1915

4 Wadsworth and others, Ball, and Jeghers, Houghton and Foley

5 Inada

6 McDowell, Bates, Ball, and Jeghers, Houghton and Foley

7 Wadsworth and others and Blumer

8 Wadsworth and others

fact that jaundice is only a symptom occurring in the course of many infectious diseases and that when the exact nature of the infectious disease is not known the condition is simply called infectious jaundice. Epidemic infectious jaundice may well be a definite entity the exact cause of which has not been found, despite many thorough investigations.

Weil's disease is an entity with a definitely known cause. The source of infection, rat infestation with *L. icterohaemorrhagiae* pathogenic for guinea-pigs, is known to be generally distributed over the entire United States.⁹ The organisms described in this country are considered identical with those in Europe and Japan. *Leptospira* represents a type of spirochete and differs from *Spirochaeta pallida* in that the spirals are more numerous and more tightly coiled. The most characteristic morphologic feature of *L. icterohaemorrhagiae* is its sharp, tapering, hooked ends, which are set at an angle to the main axis, giving the whole organism a resemblance to the letter C or S. The organism has been fully described and successfully cultivated by Noguchi.²

Norwegian and black rats and mice constitute the essential source of *Leptospira*. Probably through contamination with the urine of these animals water and slime have also been found to harbor the organism. The rat is a carrier and is not subject to the disease. Not all strains of *Leptospira* are pathogenic, particularly those found in water or slime, but the virulence can usually be raised by passage through a guinea-pig or a human being, so that the organism becomes pathogenic.¹⁰ Pathogenic leptospiaras may remain alive for months in a suitable natural environment, such as wet ground soil from a mine or in pit water.¹¹ Adequate drainage and changing the soil reaction to mildly acid have been found to eradicate the organism.¹² This point was noted on the western front during the World War, as the soldiers in adequately drained trenches and bases were free from spirochetel jaundice.¹³ In 1914 Wolbach and Binger found spirochetes morphologically similar to *L. icterohaemorrhagiae* in stagnant natural water. Since then this organism has been found in natural water throughout the world and is known as *Leptospira biflexa*, it is nonpathogenic. Pathogenic strains, other than *L. icterohaemorrhagiae* known at present include *Leptospira hebdomadis*, the cause of Japanese seven day fever, *Leptospira grippotyphosa*, the cause of the swamp fever of eastern Europe, and *Leptospira canicola*, which produces in dogs a disease similar to Weil's disease.

9 Wadsworth and others, Noguchi, 1917, Jobling and Eggstein, Neill, and Otteraaen

10 Baermann and Zuelzer

11 Buchanan

12 Inada and others, 1916, and Ido, Hoki, Ito and Wani

13 Stokes, Ryle and Tytler

The mode of transmission of this disease from infected rats or water to man is not definitely known. The disease has been reported as occurring after a rat bite,¹⁴ handling a culture of the organism and becoming infected through a needle prick of the skin⁸ and after falling into a ditch of liquid manure and swallowing some of the material.¹⁵ Direct contact was considered responsible for the spread of the disease in cases occurring among children.¹⁶ Uhlenhuth and Zuelzer have stated that oral infection in man is exceedingly unlikely because the leptospiras are rapidly killed by the acid of the gastric juice and by the bile of the intestine. Japanese investigators¹⁴ have reported the production of the disease in guinea-pigs by the oral administration of the organism and also by the application of the infectious material on abraded and on unabraded skin. Experimentally this disease has been transmitted to the guinea-pig by the house-fly,¹⁷ stable-fly,¹⁸ bedbugs¹⁹ and possibly by *Aedes Aegypti*.²⁰ Among the types of workers frequently mentioned in connection with this disease are sewer workers, butchers, mine workers, fish cutters, rice-field workers, workers in breweries and slaughter houses, barge-men and soldiers (World War).

Inada divided the disease into three stages, namely, a first, or febrile, stage, a second, or icteric, stage and a third, or convalescent, stage. The first, or febrile, stage is characterized by the usual symptoms of an acute infectious disease. It continues from the onset to about the seventh day. The main symptoms, initiated with chills and high fever, are intestinal disturbances, headache, cramping muscular pains, marked hyperemia of the conjunctivae and albuminuria. Death rarely occurs during this stage. Dark field examination of the blood demonstrates the presence of leptospiras. The organisms are also excreted in the urine in this stage, and the injection of urine into guinea-pigs results in a typical reaction. From the fourth day on there is gradual disappearance of the organisms from the blood stream. This is due perhaps to the action of antibodies in the blood. The second, or icteric, stage continues for about one week. As a rule there is a gradual subsidence of the symptoms of the first stage, and jaundice, hemorrhagic diathesis, marked general weakness, nervous symptoms and cardiac weakness develop. Most deaths occur during the second stage. The third or convalescent, stage begins about the end of the second week. The

14 Ido, Hoki, Ito and Wani

15 Schurer and Stirl

16 Lyon and Buchanan

17 Reiter

18 Uhlenhuth and Kuhn

19 Blanchard, Lefrou and Laigret

20 Noguchi, 1919, Gav and Sellards, Schuffner and Mochtar, and Aitken, Connal, Gray and Smith

jaundice subsides, and anemia and marked emaciation become prominent. *Leptospiras* completely disappear from the blood, owing to the further development of antibodies. Increasing numbers of organisms are excreted in the urine, so that by the nineteenth or twentieth day dark field examination of the urine usually reveals their presence. From the twenty-fifth day the number of patients showing organisms in the urine decreases. By the fortieth day practically all patients are free from the organisms. There frequently occurs during the third stage a recurrence of fever. The fever is markedly remittent, and Inada said he prefers to call it an after-fever rather than a relapsing fever, for the

TABLE 1—*Signs and Symptoms in the Twenty Cases of Weil's Disease Reported in the United States and Canada*

Signs and Symptoms	Previously Reported Cases													Our Cases						
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
Initial chill	0	?	+	?	+	+	+	+	+	0	?	+	+	0	0	0	0	0	0	0
Fever	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	0	0	0	+	0
Jaundice	0	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestinal disturbances	+	+	?	?	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous symptoms	?	+	?	+	+	+	+	+	+	+	+	?	+	+	0	+	+	+	+	+
Muscular pains	?	+	+	+	+	+	+	+	?	+	?	?	+	0	+	0	+	+	0	0
Conjunctival congestion	?	?	0	0	+	0	?	?	0	0	?	?	+	0	+	0	0	0	0	0
Hemorrhagic diathesis	?	+	?	+	+	+	+	+	?	0	?	+	+	+	+	0	0	+	+	+
Enlargement of the liver	?	?	0	+	+	+	+	+	+	+	+	+	+	0	+	0	+	0	0	0
Palpable spleen	?	?	0	0	0	0	0	0	+	0	0	0	0	0	0	0	+	0	0	0
Leukocytosis	+	?	?	0	+	+	+	+	+	+	+	0	+	0	0	0	+	0	0	0
Achylia	?	?	?	?	?	?	?	?	?	?	?	?	?	?	?	0	0	?	0	?
<i>Leptospiras</i> in blood	+	0	+	?	?	+	0	?	?	0	?	?	?	+	+	+	+	+	+	+
<i>Leptospiras</i> in urine	?	0	?	?	?	?	0	?	?	0	?	?	?	0	0	0	0	0	0	0
<i>Leptospira</i> in sections at autopsy	?	+	?	?	+	?	?	?	?	?	+	+	+	?	0	?	?	0	?	?
Positive result of guinea pig test	+2	0	?	+1	?	+2	+2	+1	+1	+2	+4	0	?	+	+1	+1	+2	+2	?	?
Direct van den Bergh reaction	?	?	?	+	+	?	+	?	?	+	+	0	?	+	+	+	+	0	+	+
Outcome	R	D	R	R	D	D	R	R	R	R	D	D	D	R	D	R	R	D	R	R

In this table 0 indicates absence of the symptom or sign, +, its presence, ?, no mention or the test was not done, D, death, R, recovery. 1, using the urine of the patient, 2, using the blood of the patient, 3, using the cerebrospinal fluid of the patient, 4, using macerated renal tissue from the patient.

reason that none of the signs or symptoms essential to a diagnosis of the original disease is present. The cause of the recurrence is still in doubt. The symptomatology for all the cases reported in the North American literature, including the present series, appears in table 1 and figure 1.

Dawson, Hume and Bedson have studied the pathologic picture of this disease. They found that the principal pathologic changes are confined to the abdomen, especially the duodenum, the liver and the kidneys. The duodenum has shown a definite inflammatory reaction, most marked about the ampulla of Vater. The bile ducts are generally normal, except in the last $\frac{1}{2}$ inch (1.5 cm.) of the common duct lying within the duodenal wall. This is found to be swollen, resembling the inflammatory condition in the duodenum. In one patient a plug was

found obstructing the outlet of the common duct This is mentioned especially because of the pathologic picture presented by our second patient

The liver is usually normal on gross examination, except that it is bile stained Microscopically the pathologic picture varies greatly Occasionally the organ is normal Again there may be seen both hypertrophy and hyperplasia Bates observed both minute and large areas of necrosis There may be a small amount of leukocytic infiltration

The kidney is usually swollen, and the capsule is tensely stretched The cells of the tubules are swollen and degenerated or necrotic The

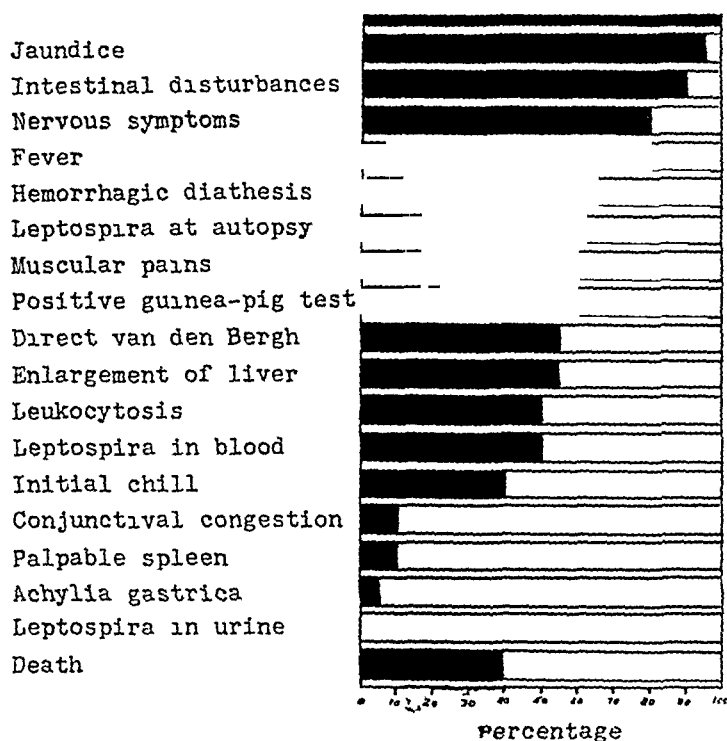


Fig 1.—The frequency of various signs and symptoms as noted in twenty cases of Weil's disease The black column indicates the percentage of patients showing the symptom

glomeruli are congested, and their cells are degenerated There are scattered collections of polymorphonuclear leukocytes in and between the tubules Hemorrhages occur into the lumen of the tubules

No other organs are typically affected The lungs may occasionally show hemorrhagic areas, but this has been noted less frequently in human beings than in inoculated guinea-pigs Bates reported that the skeletal muscles, particularly those of the calf, present evidence of hyaline degeneration and necrosis of the fibers, with surrounding inflammatory infiltration The pathologic picture, in brief, is that of jaundice, hemorrhages due to capillary damage and the congestion and

necrosis of the liver and kidneys as it occurs in any acute infection. The appearance is not so distinctive as to permit a pathologic diagnosis without the aid of other studies.

The guinea-pig, about six days after intraperitoneal inoculation with infected blood or urine, has a fever and becomes toxic and then jaundiced. It usually dies the tenth day or later, depending on the presence of immune bodies in the blood. At necropsy, besides recovery of the organism from the blood, urine, liver and kidney, the following pathologic picture is usually noted: generalized icterus, petechiae, hemorrhages in the lungs, acute congestion of the kidneys, with minute hemorrhages and large hemorrhages in the adrenal glands.

Weil's disease is usually given consideration only in cases of acute febrile jaundice. In view of our experience we believe that this disease should be considered in every case of unexplained jaundice. The diagnosis cannot be made on clinical evidence alone and must be confirmed by at least one of the following methods: first, dark field examination or smear of blood showing *L. icterohaemorrhagiae*, second, the demonstration of *L. icterohaemorrhagiae* in the urine, third, injection of blood or urine into the guinea-pig, with subsequent production of typical lesions and recovery of the organism, and fourth, the demonstration of specific antibodies in the blood either by means of the Pfeiffer reaction or by direct agglutination with a known strain.²¹ This last reaction has been obtained twelve years²² and even twenty-two years²³ after the original illness. Less important methods of diagnosis, as mentioned by Jeghers and his associates, include culture of the patient's blood,²⁴ complement fixation test (Gaetgens),²⁵ the precipitation test²⁶ and the adhesion test.²⁷

In our experience examination of the blood by direct dark field examination was the most satisfactory method of diagnosis and gave positive results for all our patients. Some had as high as 25 organisms per high power field, and in none was the search time-consuming, for practically every field contained a few of the organisms. The urine was examined, but leptospiras were not found by this method. An exhaustive search was not made in any case because organisms were demonstrated in the blood. In four of our seven cases the diagnosis was confirmed not only by examination of the blood but by guinea-pig inoculation with blood in two cases and with urine in two other cases,

21 Schuffner

22 Fairley

23 Uhlenhuth and Fromme 1930

24 Manteufel

25 Gaetgens

26 Hindle and White, and Lusena and Carlinfant

27 Brown

with positive findings. It is to be noted that our second and seventh patients possibly had had the disease for eight months before the diagnosis was made and confirmed, also that for our third and fourth patients leptospiras were easily demonstrable in the blood for nine and five weeks respectively.

The disease is so little known in this country and the clinical picture so variable that to mention a list of diseases which it may resemble is useless. Weil's disease must often be suspected on minimal grounds, and the suspicion must be confirmed or rejected by laboratory examination. In the patients reported on in North America jaundice was present and furnished the basis for the laboratory examination in all except the first case.⁸ However, as pointed out by Jeghers, this symptom is often not mentioned in case reports from Europe and Japan and therefore cannot form the only basis for suspecting the presence of the disease. Any of the listed symptoms, especially clamping muscular pains, hemorrhagic diathesis and enlargement of the liver, in the absence of other adequate explanation, may be important leads.

The prophylactic treatment with immune horse serum in countries where the disease is endemic has been successfully used. In the treatment of patients with active involvement convalescent serum and immunized horse or goat serum are equally effective. The mortality rate from this disease in Japan has been materially reduced by the use of immune horse serum.²⁸ Rabbit serum has been used by Uhlenhuth and Fromme²³ in epidemics because they found it possible to produce antibodies in the blood of the rabbit more quickly than in that of the horse or goat. Polyvalent serum is preferable because of the heterogeneity of the organism.²⁹

Convalescent whole blood from our third patient was used in the treatment of our fourth patient. The initial injection resulted in a diminution in the number of organisms, but a second injection was necessary before the organisms disappeared entirely from the blood. Convalescent serum was used for our fifth, sixth and seventh patients, with prompt disappearance of the organisms from the blood.

Arsphenamine and other arsenicals are said to be worthless as aids in the treatment, according to standard textbooks and articles. Inada and his co-workers¹ have shown that the leptospiras are removed from the blood of the guinea-pig by arsphenamine though not as effectively as with convalescent serum or immunized goat or horse serum. One of the principal objections to the use of an arsenical is that it may increase the hepatic damage. Our third patient was shown to have leptospiras in the blood after sixty days, though during the previous thirty days the liver had shown no damage either clinically or by laboratory tests.

28 Inada, Ido, Hoki, Ito and Wani

29 Baermann and Smits

Neoarsphenamine (0.3 Gm.) was given intravenously at this stage, and leptospiras were not again demonstrable in the blood or urine. This prompt result could hardly have been coincidental.

REPORT OF CASES

CASE 1—M. A., a printer aged 32, was admitted to the hospital on Jan. 7, 1932. The chief item of interest in the history was that he had worked and lived in many places. At the onset of the illness he was living in a cheap hotel, which he stated was rat infested. On January 1 he had cramplike pains in the upper portion of the abdomen, with moderate nausea and vomiting. The following day he felt improved, but a day later there was a recurrence of the original symptoms, accompanied with diarrhea. The patient next noted that the urine was "strong and burned" and that there was considerable frequency. He was restless and did not sleep well. Pyrosis became marked. On January 6 he first noted that his skin was yellow. Moderate cough, fever and headache developed at this time. Blood-tinged expectoration occurred the day prior to his admission to the hospital.

Examination—The patient was acutely ill, with a temperature of 103.4 F. The skin and mucous membranes were markedly icteric. The blood pressure was 112 systolic and 60 diastolic. There was noted considerable tenderness over the liver and gallbladder. The blood was examined by the dark field method the day following the patient's admission to the hospital, and many leptospiras were observed in each high power field. Two guinea-pigs were inoculated intraperitoneally with the patient's urine on January 8. The pigs died on January 23 and 24, respectively. They had been acutely ill and had showed jaundice; leptospiras were recovered. Dark field examination of the patient's urine did not reveal leptospiras. The icterus index on January 8 was 80, and on January 24 it was 45. The van den Bergh test showed a prompt direct reaction. The Wassermann and Kahn reactions of the blood were negative. The white blood cell count was 7,900, with 64 per cent polymorphonuclears. The red blood cell count was normal. Repeated urinalysis revealed no abnormality except for the presence of bile.

Course—The temperature ranged from 99.8 to 103.4 F. for three days after the patient's admission to the hospital, and thereafter it was normal except for an occasional reading of 99 F. The pulse rate was always under 100 and usually under 90. The blood no longer showed leptospiras after about the tenth day of illness, and the urine gave a negative response to guinea-pig inoculation after the twenty-first day. The jaundice and the tenderness in the right upper quadrant of the abdomen subsided more slowly, but recovery was complete. Treatment was symptomatic.

CASE 2—E. V. M., a Negro automobile mechanic aged 37, was admitted on Jan. 19, 1935. He had lived in Denver for the past two years and had been in good health until May 1934, eight months prior to admission to the hospital. At that time he commenced to feel sluggish, had no energy and became nauseated and vomited soon after eating. A few days later he noticed that the stools were light clay colored, and they remained so. The urine became dark and the eyeballs were yellow. Coincident with the appearance of jaundice the patient had a feeling of discomfort in the right upper quadrant of the abdomen. The pain was dull. There was no sharp or colicky pain at any time. The jaundice increased steadily until August and then remained about the same. Itching of the skin had been present since July. Throughout this illness the patient worked steadily at his usual

occupation until two weeks prior to his admission to the hospital. At various periods during the eight months there was aching of the muscles, particularly in the calves of the legs. There was a total loss of 37 pounds (16.8 Kg). Constipation, not present originally, became a prominent symptom during the month preceding his admission to the hospital. The appetite remained good, but the patient refrained from eating because of postprandial gaseous distention.

Examination—The patient was ambulatory, afebrile, well developed and well nourished, with prominence of the upper portion of the abdomen. He did not appear acutely ill. His weight was 133 pounds (60.5 Kg), and his height was 5 feet 4½ inches (164 cm). There was marked icterus of the skin and mucous membranes. The conjunctivae were injected. The special senses were grossly normal. Mild oral sepsis due to periodontoclasia was present. There was slight generalized lymphadenopathy. The thyroid gland was normal. The tonsils were buried. The pulse beats were equal, soft and regular, with a rate of 76. The heart was normal in size and position, no thrills, shocks or murmurs were noted, and the tones were normal. The blood pressure was 116 systolic and 82 diastolic. The lungs were resonant throughout, and the breath sounds were normal. The

TABLE 2—*Chemical Study of the Blood of the Second Patient*

Date	Nonprotein Nitrogen, Mg per 100 Cc	Urea Nitrogen, Mg per 100 Cc	Cholesterol, Mg per 100 Cc	Serum Bilirubin, Mg per 100 Cc	Icterus Index	Rosenthal Test	Sugar, Mg per 100 Cc
1/22	32.6				75		77
1/24	38.0	16.5	210.0		94		
1/29					120		
1/31	28.0	14.5	196.0		85		
2/ 7	24.0	10.0	320.0	19.4	56		
2/15	28.0	11.5	418.0		100		
2/21	19.0	12.9	532.8		100	20% retention in 30 min	
2/28				42.8			
3/ 3				45.7			

entire genito-urinary system appeared normal. The abdomen was rounded, with prominence of the right upper quadrant. The liver was enlarged to 3 finger-breathths below the costal margin and was tender, particularly over the gallbladder, which appeared as a bulging mass the size of an orange, moving with respiration but not distinctly palpable. The spleen was not palpable. There were no other masses in the abdomen. The pupils were slightly irregular but reacted to light and in accommodation. The superficial and deep reflexes were normal. There was no Babinski or Romberg sign or any sensory disturbance. The cranial nerves were normal. The skeletal system was grossly normal. The muscles of the calves were tender to pressure.

Laboratory and Special Examinations—The results of the chemical studies of the blood are given in table 2. The van den Bergh test gave a prompt direct reaction. The clotting time was three minutes, but it fluctuated between two and five minutes until February 21, when it was eighteen minutes. On March 5, the day prior to operation, the clotting time was seven and one-half minutes. On January 21 the blood was examined by the dark field method and found to be teeming with leptospiras. That day a guinea-pig was inoculated intraperitoneally with the patient's blood. On January 29 the pig died, and autopsy showed icterus and generalized hemorrhages. Leptospiras were easily recovered. The blood was examined for organisms on three other occasions, but none was found. The urine

showed no organisms by dark field examination, and except for moderate albuminuria and a bile-stained color, it was normal. The urinary output was increased, on one occasion being 4,000 cc in twenty-four hours. The stools showed no ova or parasites, but occult blood was present. The red blood cell count prior to operation varied from 4,200,000 to 3,300,000. After operation the count fell and was 2,200,000 the day preceding death. The white blood cell count was low, varying from 3,700 to 6,500 before operation. Thereafter there was a sharp rise to 13,000 and later to 17,000, on the day of death. The differential count showed constant eosinophilia, with 3 per cent or more and on one occasion 8 per cent eosinophils. The blood platelet count was 285,000. Gastric analysis by the fractional method showed achylia, with the highest total acidity 16. The Wassermann and Kahn reactions of the blood were negative.

Course—The original impression in this case was of obstructive jaundice. There was continuation of the clay-colored stools and the dark-colored urine. Because of the presence of unexplained jaundice and muscular cramps, dark field examination of the blood was carried out, and leptospiras were demonstrated. Rechecking of the history at this time in reference to contact with rats revealed that the patient had never to his knowledge been bitten by a rat, but that both his home and his place of work were rat infested. On January 25 a duodenal tube was passed, but no bile was obtained. On January 26 some yellow alkaline fluid was obtained, but on repeated drainage thereafter no trace of bile was obtained. Twenty-four hours after the patient's admission to the hospital fever developed and was intermittent from that time on, the temperature ranging from 96.4 to 102.8 F. The pulse rate ranged from 72 to 108. Symptomatic treatment included a low fat-high carbohydrate diet, duodenal drainage, with daily instillation of magnesium sulfate, hot moist compresses over the liver, alkaline water and methenamine. On February 6 a note was made that nosebleeds had been occurring for several days. Up to February 14 the patient's condition was essentially stationary, except that the liver was less tender, the urine was lighter and pruritis varied from minimal to marked. From this time on, however, the course was downward. The patient had more pain, was more toxic and had a slightly higher temperature.

Operation—Exploratory laparotomy was decided on, with a tentative diagnosis of obstruction of the common duct, possibly secondary to Weil's disease. It was thought that there was an inflammatory lesion in the common duct, particularly in the intramural part, which had caused a complete block either through inflammatory atresia or exudate. Calcium chloride was given intravenously for three days prior to operation. A transfusion of 500 cc of blood was given the day prior to surgical intervention. On March 6 the operation was performed. The liver was observed to extend below the level of the umbilicus. The gallbladder was huge and extended well below the free border of the liver. The common duct was 3 or 4 cm in diameter. The common duct was opened $\frac{3}{4}$ inch (2 cm) from the cystic duct, and 1,500 cc of bile was aspirated from the bile ducts. A probe was inserted into the distal portion of the common duct and was easily passed to the opening of the duct at the ampulla but could not be passed into the duodenum. There was evidently complete closure at that point due to growth of tissue. Choledochoduodenostomy was done.

Postoperative Course—The patient left the operating room showing evidence of severe shock, as manifested by a pulse rate of 140 and a blood pressure of 74 systolic and 44 diastolic. The course following operation continued steadily down-

ward There was continuous oozing of blood from the abdominal wound Three blood transfusions did not affect the course The patient died forty-nine hours after operation

Autopsy—The postmortem examination revealed that there was complete atresia of the intramural portion of the common bile duct, with great dilatation of the common duct, hepatic ducts and gallbladder The anastomotic orifice of the com-

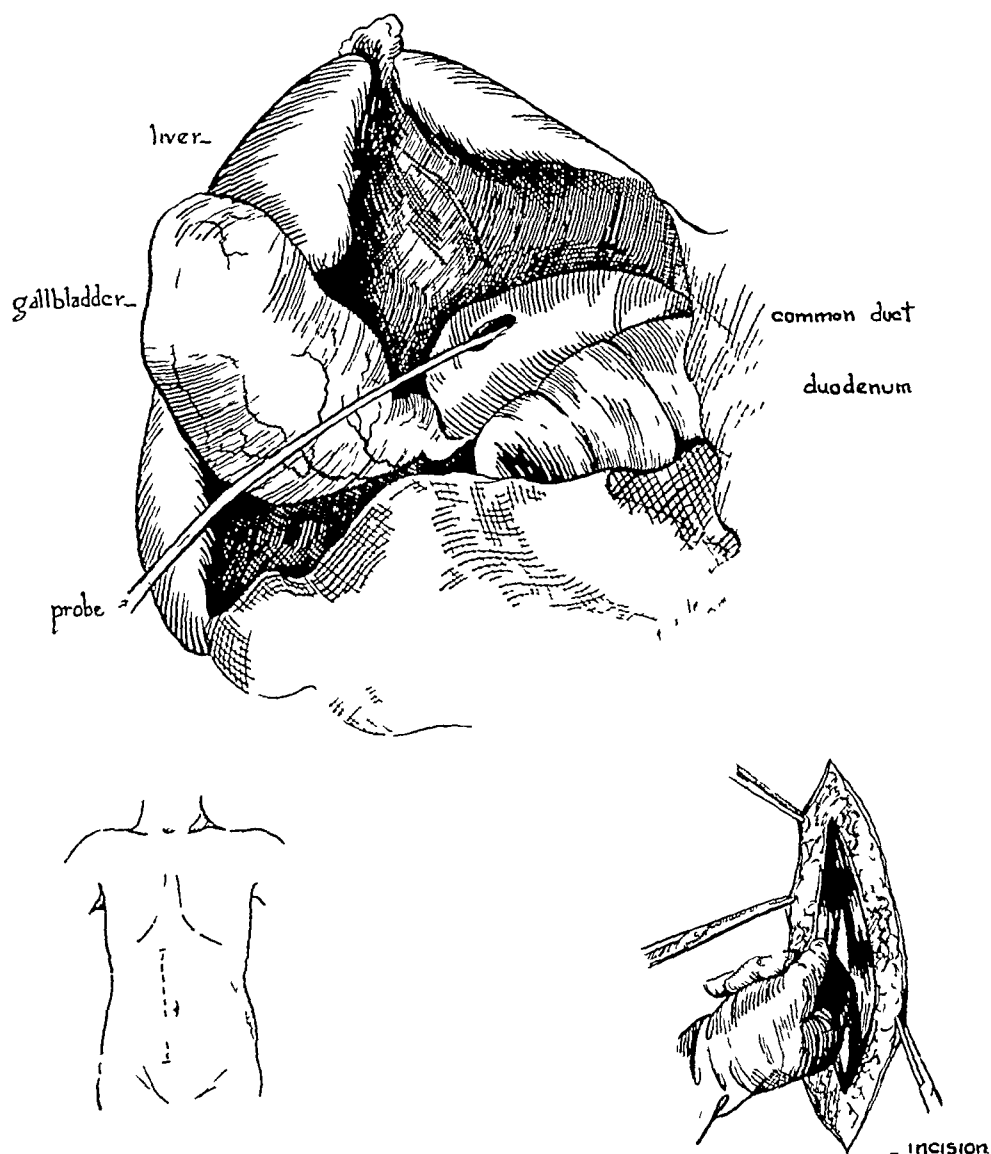


Fig 2—Weil's disease complicated by obstruction of the common duct

mon duct into the duodenum was completely occluded by a large blood clot The liver weighed 2,500 Gm and was grossly normal, except that it was somewhat yellow In the microscopic examination the hepatic cells showed cloudy swelling and scattered areas of focal necrosis Sections stained by the Levaditi method revealed no organisms Other diagnoses were (1) bilateral bronchopneumonia, (2) focal necrosis of the spleen, (3) slight chronic glomerulonephritis and (4) slight biliary cirrhosis of the liver

CASE 3—J E M, a soldier aged 22, was admitted on April 19, 1935, with complaints of headache, vomiting and yellow discoloration of the eyes and skin. The patient had been perfectly well until the evening of April 15, when he suddenly became nauseated and vomited twice. The next two days he continued on duty but felt bilious, that is, he noted headache, anorexia, nausea and lack of energy. On April 17 he noticed that his eyeballs were yellow. Because of continuance of these symptoms he entered the hospital. There had been no abdominal pain or muscular cramps, and he had no other complaints.

Examination—On admission to the hospital the patient was afebrile. He was well developed and well nourished but appeared acutely ill. His weight was 150 pounds (68 Kg), compared with his usual weight of 160 pounds (72.6 Kg). His height was 5 feet and 11 inches (180 cm). The special senses were normal. The skin and mucous membranes showed moderate jaundice. There were no petechiae or hyperemia of the conjunctivae. There was no adenopathy. The tonsils were absent. The thyroid gland was normal. The pulse beats were equal, soft and regular. The blood pressure was 114 systolic and 76 diastolic. The heart and lungs were normal, as was also the genito-urinary system. Rectal examination revealed no abnormality, and the stools were of normal color. The abdominal examination revealed no abnormality. The liver and spleen were not palpable. The other systems were normal. There was no tenderness of the muscles of the calves.

Leptospiras were demonstrated in the blood by the dark field examination on the day the patient was admitted. A guinea-pig was inoculated with the patient's blood on April 26 and died on May 6. Autopsy of the animal showed a typical picture, leptospiras were demonstrated. The icterus index at the time of the patient's admission to the hospital was 14. The following week it reached its peak of 65 and was normal again after twelve weeks. The van den Bergh test gave a prompt direct reaction. On May 6 the serum bilirubin content was 6.5 van den Bergh units, on May 15 it was 3.2 units. On April 26 the Rosenthal hepatic function test showed 12 per cent retention after thirty minutes. In the fourth week of the patient's illness there was 15 per cent retention after thirty minutes. Weekly examinations from the fifth week on showed no thirty minute retention of the dye. On May 16 the nonprotein nitrogen content of the blood was 54 mg. The following week it was 60 mg, but thereafter it was normal. The cholesterol content of the blood was 162 mg on May 16, 219 mg on June 14 and 220 mg on June 28. On entry the white blood cell count was 10,400, with 68 per cent polymorphonuclears, including 6 per cent eosinophils. Subsequent counts varied from 6,000 to 8,000, with from 3 to 6 per cent eosinophils. The red blood cell count, hemoglobin content and platelet count were normal, as were the bleeding and coagulation times. The Wassermann and Kahn reactions of the blood were negative. Fractional gastric analyses were normal. Urinalyses were normal except for a trace of albumin on occasions and also considerable bile. Specimens of urine were examined for organisms by the dark field method, but none were demonstrated.

Course—The patient appeared to have a case of typical acute catarrhal jaundice, but owing to the recent study of a patient with Weil's disease in the hospital this patient's blood was examined by the dark field method and was found to contain leptospiras. For the fifteen dark field examinations made in this case no extended search was ever necessary. There were always from 10 to 30 organisms per high power field. Duodenal intubation was always successful in obtaining bile but without the usual changes in color concentration. The stools were light during the second week of hospitalization but always contained bile. The urine was at

times heavily bile stained. The patient remained completely afebrile throughout the entire period. Except for the initial complaints when admitted to the hospital, he felt well until about the fourth week. At that time pain developed over the right upper quadrant of the abdomen, and there was slight tenderness over the edge of the liver. However, there was no enlargement of the liver or spleen. The discomfort in the hepatic area gradually subsided and was not evident at the time of the patient's discharge. The jaundice persisted until the ninth week. For the first week there was some increase in the icterus, but thereafter it decreased rapidly until it was evident only in the conjunctivae. The patient never exhibited any evidence of a hemorrhagic diathesis.

The patient was placed on a diet high in carbohydrate and low in fat, augmented by syrup and daily ingestion of 1 quart (1 liter) of 10 per cent dextrose water. Alkaline mineral water was used. By June 18 the results of the hepatic function test of Rosenthal had been normal for the preceding five weeks, and the icterus index had approached normal. With this in mind and owing to the continued presence of leptospiras in the blood, we gave neoarsphenamine (0.3 Gm) intravenously. On the following day and thereafter, leptospiras could not be demonstrated. Recovery appeared to be complete.

CASE 4—M. K. I., a soldier aged 19, was admitted to the hospital on May 18, 1935, with chief complaints of pain in the right upper quadrant of the abdomen, muscular pains, malaise, headache and jaundice. He had been perfectly well until May 11, when malaise and anorexia developed and he vomited his supper. These symptoms continued, associated with progressive loss of energy. On May 14 he had a cramplike pain in the right upper quadrant of the abdomen, radiating into the left upper quadrant. The next day cramping pains developed in the muscles of the left calf. These muscular pains increased in severity and included both arms and both legs at the time of the patient's admission to the hospital. On May 16 he first noted that the stools were light and that the urine appeared dark. The following day a friend noticed yellowness of the patient's skin. There were no additional complaints.

Examination—The patient was a well developed and well nourished jaundiced youth, appearing acutely ill. He was afebrile and ambulatory. His weight was 132 pounds (60 Kg), and he was 5 feet and 7 inches (170 cm) tall. The special senses were grossly normal. Both the skin and the mucous membranes were moderately jaundiced. Generalized slight lymphadenopathy was present, the tonsils were absent and the thyroid gland was slightly enlarged. The pulse beats were equal, soft and regular. The blood pressure was 118 systolic and 72 diastolic. The heart and lungs were normal, as was also the genito-urinary system. Rectal examination revealed no abnormality. The abdomen was soft, and there was slight prominence of the right upper quadrant owing to enlargement of the liver, the liver extended 3 fingerbreadths below the costal margin and was tender. The gall-bladder and spleen were not palpable. There were no other masses. The nervous system, the osseous system and the muscles and joints were normal, except for marked tenderness of the muscles of the legs and arms to pressure.

When the patient was admitted the blood was examined in the dark field, and it was found teeming with leptospiras, as many as 20 to each high power field. The icterus index was 12.5 on May 18, 15.6 on May 23, 12.5 on May 27, 13.5 on June 1, 9 on June 7, 7.2 on June 11, 7.7 on June 17, 16.5 on June 22, 8.6 on June 26, 5 on July 8 and 4 on July 22. The Rosenthal hepatic function test showed 7 per cent retention after thirty minutes on May 22. On May 27 and June 1 there was no retention. On June 10 there was 5 per cent retention. From that date on there was no retention, the test being repeated weekly. The van den Bergh test

gave a prompt direct reaction. The white blood cell count ranged from 8,000 to 14,000, with a normal differential count and without any increase in the eosinophils. The red blood cell count, the bleeding and coagulation times and the hemoglobin content were normal. The stools were clay colored when the patient was admitted and remained light until August, when they again became dark. Urinalyses gave normal results, except for the presence of bile. Chemical analysis of the blood showed on May 20 66 mg of nonprotein nitrogen and on May 23 54 mg, thereafter the content was normal. On June 4 the cholesterol content was 192 mg, on June 12, 200 mg, and on June 26, 178 mg. Other determinations of the cholesterol content both before and after these dates gave normal results. The Wassermann and Kahn reactions of the blood were negative. Gastric analyses by the fractional method showed high normal curves for acidity. A guinea-pig inoculated intraperitoneally with the patient's blood died in ten days and showed the typical evidence of Weil's disease. *Leptospiras* were recovered from this animal.

Course—The patient was afebrile throughout the course of the illness, and at no time did he show any hemorrhagic tendencies. The stools remained light even after the icterus index had returned to normal. Repeated duodenal drainage resulted in the obtaining of light bile without the usual changes in color. *Leptospiras* were consistently and easily demonstrated in the patient's blood. On June 21 the patient was given intramuscularly 30 cc of convalescent whole blood obtained from our third patient with Weil's disease. The following day there was a marked diminution in the number of organisms present in the patient's blood. From a previous average of from 10 to 20 per high power field, the number dropped to 5 per field. On this day 50 cc of convalescent whole blood was again given intramuscularly, and thereafter organisms were not demonstrable in the patient's blood. Clinical improvement was also noticeable from this date. The patient stated that he felt improved and had more energy, less anorexia and less headache. There remained a subicteric tinge to the skin and scleras until the end of July. Recovery was slow but otherwise uneventful. The patient was returned to duty on August 21. It is to be noted that dark field examination of the blood was carried out weekly and *leptospiras* were easily demonstrated. This continued for the first five weeks of hospitalization, until a second injection of convalescent whole blood had been given.

CASE 5—G C D, a woman aged 42, was admitted on June 24, 1935. Her previous history showed rheumatic fever and chorea in childhood, and, except for an acute mental disturbance following the death of her husband in 1932, she had been apparently perfectly well until September 1934, nine months prior to her admission to the hospital, when she noticed swelling of the feet and ankles and moderate dyspnea on exertion. In May 1935 the patient's mother, from whom most of the history was obtained, noted a yellow cast to the patient's eyeballs and later a general yellow tinge of the skin. In the early part of June gastro-intestinal symptoms in the form of nausea and vomiting appeared. Little food was retained, and there was marked loss of weight and strength. Pain was not present at any time. Up to June 17 the patient had been under chiropractic treatment, but on this date the mother called a physician, and the patient was promptly sent to a hospital and treated mainly for congestive heart failure. A flat roentgenogram of the abdomen taken did not show gallstones. On June 24 the patient was transferred to this hospital. The tentative diagnosis of the physicians in charge was that of heart disease and possible carcinoma of the gallbladder or pancreas, the latter diagnosis being based mainly on the increasing painless jaundice.

Examination—The patient appeared extremely ill. She was of normal development, with marked anasarca and jaundice. The skin was moist and cool, and there were several large ecchymotic spots on the arms, legs and back. There was no adenopathy. The pulse was decidedly irregular in force and rhythm but was soft. The blood pressure was 110 systolic and 70 diastolic. The heart was moderately enlarged by percussion both to the right and to the left. A systolic murmur was heard over the entire precordium but with maximum intensity over the apex. No thrill was palpable. Numerous coarse moist râles were scattered throughout both lungs. Moderately severe internal and external hemorrhoids were present. The edge of the liver was just palpable and was markedly tender. The tendon reflexes were absent. Pressure on the calves of the legs elicited severe pain.

On the day of the patient's admission to the hospital dark field examination of the blood revealed numerous leptospiras. They were also present on June 26. The icterus index was 90, on June 28 it was 81.8. The van den Bergh reaction was diphasic. On June 26 the Rosenthal hepatic function test showed 45 per cent retention of the dye after thirty minutes. The nonprotein nitrogen content of the blood was 31 mg, and the cholesterol content was 256 mg. All specimens of urine showed considerable albumin and bile, but leptospiras were not demonstrable. The red blood cell count was 5,100,000, and the hemoglobin content was 90 per cent (Tallqvist). The white blood cell count was 9,100, with a normal differential count. The platelet count was 255,000. The coagulation and bleeding times were normal. The Wassermann and Kahn reactions of the blood and spinal fluid were negative. The spinal fluid was icteric but was otherwise normal, and leptospiras could not be found. An electrocardiogram confirmed the clinical impression of auricular fibrillation.

Course—At the time of admission to the hospital the patient was moribund, and she remained semicomatose and afebrile until death occurred on the sixth day. The treatment in this case was directed mainly toward the relief of cardiac failure. On June 26 she was given intramuscularly 25 cc of convalescent serum from our fourth patient with Weil's disease, and while leptospiras were not again found in the blood, no other effect was noted. The clinical diagnosis was spirochetal jaundice and decompensated rheumatic mitral stenosis with auricular fibrillation.

Autopsy—Autopsy revealed generalized ecchymosis of the skin and numerous submucosal and parenchymal petechiae. There was rheumatic mitral stenosis, the heart weighing 360 Gm. The liver was of normal size, yellowish gray and extremely soft and greasy. Microscopic examination of the liver showed severe midzonal fatty degeneration. The bile ducts and the duodenum were normal. An acute splenic tumor was present.

CASE 6—J. T. K., a soldier aged 34, was admitted on Feb. 6, 1931, for the treatment of active pulmonary tuberculosis. He was still a patient in this hospital with the tuberculosis well under control when, on May 30, 1935, epigastric discomfort developed. On June 20 it was noticed that he was jaundiced. There had been a loss in weight of 20 pounds (9 Kg.) in these three weeks. From June 23 to August 18 the patient had a low grade fever, the highest temperature being 100.2 F and the average being 99 F in the afternoons. The patient had not had any fever since shortly after his admission to the hospital in 1931. He was acutely ill, with marked abdominal discomfort associated with nausea and frequent vomiting from June 20 to July 9. Moderate, easily controllable epistaxis occurred several times during this period.

Examination—The patient was well developed and well nourished but appeared acutely ill, with marked jaundice. He weighed 158 pounds (72 Kg.) and his

height was 5 feet and 11 inches (180 cm) Phrenic exeresis and artificial pneumothorax were noted on the right side The rest of the physical examination revealed only the presence of generalized abdominal tenderness The liver, gallbladder and spleen were not palpable

On June 25 dark field examination of the blood disclosed numerous leptospiras Search of the urine, saliva and duodenal contents revealed no organisms The white blood cell count varied from 4,400 to 6,500, with a normal differential count The red blood cell count and hemoglobin content, as well as the coagulation and bleeding times, were normal Urinalyses showed a faint trace of albumin several times during the febrile period and on one occasion several finely granular casts The gastric analysis gave normal results The Wassermann and Kahn reactions of the blood were negative The van den Bergh test gave a prompt direct reaction

The results of the other laboratory studies are shown in table 3

Course—On June 26 the patient was given intramuscularly 25 cc of convalescent serum from our fourth patient with Weil's disease From that date on no leptospiras were demonstrated in the blood However, the patient continued

TABLE 3—*Chemical Study of Blood of Sixth Patient*

Date	Nonprotein Nitrogen, Mg per 100 Cc	Cholesterol, Mg per 100 Cc	Bilirubin, Mg per 100 Cc	Icterus Index	Rosenthal Test, Retention in 30 Min, %
6/26	35	560	11	89	40
7/ 2	54	189	32	95	50
7/10	38	183	11		55
7/16	31	175	19	110	45
7/24	31	165	29	100	55
7/29	34	172	19	50	15
8/14	29			50	0
8/21	36	144		20	0
8/27	30	168	1	10	0
9/ 3	31	169	Normal	9	0
9/24				6	
10/28				4	

to be very ill for practically one month, with symptoms of severe hepatic damage Recovery was eventually complete and without demonstrable effect on the tuberculous process

CASE 7—R C P, an officer aged 40, was admitted to the hospital on Nov 7, 1934, with complaints of nausea, vomiting, weakness and epistaxis of two days' duration, associated with mild diarrhea

Examination—Physical examination revealed only slight jaundice and moderate tenderness over the gallbladder The patient was thought to have a low grade infection of the gallbladder The temperature was not elevated except on the first evening, when it was 100.8 F The Graham-Cole test gave an abnormal response, in that the gallbladder did not empty well after the fatty meal The other laboratory and roentgenographic studies gave normal results, except for an icterus index of 7.5

Operation—On December 5, with the patient under spinal anesthesia, cholecystectomy was performed The gallbladder was of the usual white type The glands along the cystic and common ducts were remarkably large The ducts were normal, and no stones were present General exploration revealed no abnormality The pathologic report stated that section through the bulbous portion showed the unusual picture of a perfectly normal gallbladder, there being no erosion and no

evidence of old or recent inflammation, the mucosal fimbria being perfectly normal. Section near the outlet, however, showed a moderate fibrous infiltration but no recent inflammatory reaction.

Course—The patient made an uneventful recovery and on Jan 21, 1935, was discharged for one month's sick leave. He returned to duty on February 27. He stated at the time of discharge that he did not feel entirely normal. On July 1 he was readmitted to the hospital complaining that he had not felt perfectly well since his operation. He felt bilious, that is, he had anorexia, slight nausea, frequent headaches and lack of energy. At this time the patient was afebrile and slightly icteric. Dark field examination of the blood showed it teeming with leptospiras. The red blood cell count was 4,800,000, and the hemoglobin value was 85 per cent (Tallqvist). The bleeding and coagulation times were normal. The white blood cell count was 7,800, with a normal differential count. The icterus index on July 1 was 17.6, on July 5, 9.2, and on August 13, 12. The van den Bergh test showed a delayed direct reaction. The Rosenthal hepatic function test showed no retention of dye after either five or thirty minutes. On July 1 chemical analysis of the blood showed nonprotein nitrogen, 75 mg, cholesterol, 123 mg and sugar, 92 mg. The urine, feces and sputum contained no leptospiras.

On July 2 the patient was given an intramuscular injection of 25 cc of convalescent serum from our fourth patient with Weil's disease. On July 3 leptospiras were still demonstrable in the blood, but there were fewer than on the previous examination. On July 5 and thereafter, dark field examination revealed no organisms. This patient was returned to duty on August 13. He was not entirely recovered and complained of weakness and lack of energy. Various features of the case led to a neuropsychiatric consultation, the opinion was expressed that the patient showed an introverted personality but that no real neuropsychiatric pathologic condition was present. His wife's illness and the care of one child were undoubtedly features contributing to a certain amount of mental and physical depression in this case. While leptospiras were first discovered in July 1935, symptoms of a similar nature were noted eight months before this date. It is impossible to state definitely that Weil's disease was present when the patient was first admitted to the hospital, but the symptoms were suggestive. If leptospiras were present, then the duration of the disease in this case, as in our second case, was much longer than is ordinarily thought possible in Weil's disease.

SUMMARY

The pertinent literature on Weil's disease has been reviewed. The important symptoms of the thirteen patients previously reported on in North America and of our own series of seven patients are shown in table 1 and figure 1. The relationship of Weil's disease to infectious jaundice has been discussed. The diagnosis and treatment have been considered, with particular attention to our own results of treatment with neoarsphenamine intravenously and convalescent whole blood and serum intramuscularly. Reports on our seven patients are given. The most unusual feature was the typical painless obstructive jaundice of eight months' duration noted in our second patient at the time of his admission to the hospital. Operation and autopsy in this case revealed complete inflammatory atresia of the intramural portion of the common

bile duct secondary, presumably, to Weil's disease. The third patient showed an afebrile course, and leptospiras were demonstrable in the blood by dark field examination for nine weeks. Our fourth patient also was afebrile throughout, and leptospiras were demonstrable for five weeks. Our fifth patient appears to be the only woman with Weil's disease reported on in the North American literature, except in one instance of accidental laboratory infection.⁸ Our seventh patient showed an afebrile course and was ambulatory for a period of eight months before the diagnosis was made, cholecystectomy was performed during this period without benefit.

CONCLUSIONS

The diagnosing of Weil's disease in seven cases, six of them being noted within a period of six months, indicates that this condition may not be rare.

Because of the fact that five of our patients showed an atypical course, according to the standard textbook picture, we believe that this disease should be considered more often when there is unexplained jaundice.

The source and mode of infection in these cases have not been determined. This is true not only for our series but also for the previously reported cases in North America, except for one instance of accidental laboratory infection.

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INFLUENCE OF FAT ON CONCENTRATION OF SUGAR IN BLOOD AND IN URINE IN DIABETES MELLITUS

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The discovery of insulin brought about a revolution in the dietary management of diabetes mellitus. Whereas in the preinsulin era the low carbohydrate-high fat diet was universally employed, now the majority of authorities advocate the high carbohydrate-low fat diet. Indeed, the revolution has been even more marked. In the preinsulin era carbohydrate was considered the *bête noire* of diabetic patients, now this rôle has been assigned by some investigators to fat. The advent of insulin made possible the discovery of certain fundamental principles of the metabolic disturbance in diabetes mellitus. The subject, however, is still to a large degree in a bedeviled and controversial state. In this paper the literature of the subject will be reviewed and discussed, and some experimental work will be reported.

In 1923 Allen¹ reported the results of an exhaustive study of this subject with a large number of patients and stated the following fundamental conclusions: 1. Fat causes glycosuria out of all proportion to the dextrose content. It seems important chiefly through the number of calories which it furnishes rather than as a theoretical source of dextrose. 2. This action of fat is most prompt and obvious in the cases of severest involvement, in cases of mild diabetes it may take weeks or months to make its appearance. 3. The insulin requirement of the organism is governed not only by carbohydrate but by fat and all other elements entering into the diet. 4. It remains uncertain whether insulin is directly concerned in total metabolism or specifically related to the assimilation of dextrose alone and only in some secondary or indirect manner with the metabolism of other foods.

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1. Allen, F. M. Influence of Fat and Total Calories on Diabetes and the Insulin Treatment, *J. Metabolic Research* 3: 61, 1923.

Adlersberg and Porges² have written extensively on this subject during the past decade. Their concept is based on the theory that ingestion of large quantities of fat causes infiltration of the hepatic cells with fat and that a fatty liver can less easily take up dextrose to form glycogen than a glycogen-rich liver. They stated that a diet poor in carbohydrate increases the activity of the pancreas and gives rise to an improvement in tolerance for carbohydrate. Experimentally they demonstrated the following facts: 1. Addition of fat to a maintenance diet causes a marked increase in glycosuria which takes days to develop. 2. Equicaloric substitution of carbohydrate for fat in a diet improves the tolerance of the diabetic patient and makes the insulin requirement less. 3. The conception that undernutrition improves the tolerance and that overnutrition lowers it is untenable. Overnutrition with fat reduces the tolerance, but such is not the case with carbohydrate.

Of great importance is the finding that equicaloric (Adlersberg and Porges² and Gray and Sansum³) or equigram (Richardson⁴) substitution of carbohydrate for fat may be carried out without causing an increase in insulin requirement, and at times it may even permit a reduction in the dosage. Richardson⁴ has stated: "Carbohydrate seems to use insulin for its own metabolism, but whether fat also uses insulin for this purpose, or whether it in some way inhibits the use of the insulin by the carbohydrate we do not know." Barach⁵ has expressed the opinion that 1 Gm of fat creates the need for as much insulin as 2 Gm of carbohydrate.

There are eminent students of the disease who entertain opinions which are diametrically opposed to those just presented. Thus, Newburgh and Waller⁶ have presented studies from which they concluded

2 Adlersberg, D, and Porges, O. Zur Theorie und Praxis der kurativen Diabetesbehandlung, *Klin Wchnschr* **5** 1451, 1926, Weitere Erfahrungen über die Behandlung des Diabetes mellitus mit fettarmer Diät, *ibid* **6** 2371 (Dec 10) 1927, Ueber die Diätbehandlung der Zuckerkrankheit mit fettarmer Kost. Kohlehydrat-Mastkuren bei unterernährten Zuckerkranken, *ibid* **7** 1503 (Aug 5) 1928. Adlersberg, D. Fettreiche oder fettarme Ernährung des Diabetikers? *Zentralbl f inn Med* **53** 401 (April 2) 1932. Adlersberg, D, and Porges, O. Ueber kurzfristige Behandlung der Zuckerkrankheit mit fettarmer, kohlehydratreicher Kost unter gleichzeitiger Insulinanwendung, *Med Klin* **28** 1386 (Sept 30) 1932.

3 Gray, P. A., and Sansum, W. D. Higher Carbohydrate Diet Method in Diabetes Mellitus, *J A M A* **100** 1580 (May 20) 1933.

4 Richardson, R. High-Carbohydrate Diets in Diabetes Mellitus, *Am J M Sc* **177** 426, 1929.

5 Barach, J. H. Lower Fat Diet in Diabetes, *J A M A* **98** 1265 (April 9) 1932.

6 Newburgh, L. H. and Waller, D. S. Studies of Diabetes Mellitus. Evidence That Disability Is Concerned Solely with Metabolism of Glucose, *J Clin Investigation* **11** 995, 1932.

that the ability of a diabetic patient to dispose of the available dextrose of a diet is unrelated to either the fat or the total energy content of the diet. This holds for long and for short periods of experimentation. Falta⁷ has rejected the contention that the tolerance improves only with a low fat-high carbohydrate diet. He has claimed that an equal improvement can occur with a high fat-low carbohydrate diet.

The protagonists of the high carbohydrate-low fat diet have laid great stress on the fact that if a normal person is placed on a pure fat diet for several days a dextrose tolerance test performed immediately afterward shows a blood sugar curve which is higher than normal. Indeed, this is one of the most important arguments advanced by Adlersberg and Porges⁸ for their conception of the metabolic disturbance in diabetes mellitus. Himsworth⁹ found that the administration to a normal rabbit of a diet rich in fat decreases the sugar tolerance, retards and diminishes the action of insulin on the blood sugar, prevents or delays the progressive improvement of sugar tolerance which occurs with the injection of consecutive doses of dextrose and impairs the ability of insulin to diminish the hyperglycemia following the intravenous injection of dextrose. It seems to us that this argument is not well founded and cannot be applied to diabetes mellitus for the following reason. It is well established that a dextrose tolerance test will show an elevated blood sugar curve in normal persons after fasting equal to that of normal persons who have been receiving a high fat diet. Starvation, however, instead of producing a depreciation of tolerance for carbohydrate in diabetic patients, causes an increase. Fasting constituted a basic method of treatment of diabetes in the preinsulin era. This, it appears to us, is cogent evidence that it is fallacious to apply results of experiments on normal persons to diabetic patients. MacKay and Bergman¹⁰ found that in the rat a preceding diet composed chiefly of fat was without influence on subsequent deposition of glycogen in the liver or muscles.

Of late there has been a renewal of interest in the influence of fat on the blood sugar level during fasting. Hirsch-Kauffmann and Knauer¹¹ found that administration of fat (50 cc of olive oil) to normal children

7 Falta, W. Ueber die Frage der Fettzufuhr in der Diabetesbehandlung, *Wien med Wchnschr* **82** 1291 (Oct 8) 1932.

8 Adlersberg, D., and Porges, O. Fett-nahrung und Kohlehydrattoleranz, *Med Klin* **27** 1783 (Dec 4) 1931.

9 Himsworth, H. P. Dietetic Factors Influencing Glucose Tolerance and Activity of Insulin, *J Physiol* **81** 29 (March 29) 1934.

10 MacKay, E. M., and Bergman, H. C. The Influence of the Preceding Diet upon the Rate of Glucose Absorption and Glycogen Synthesis, *J Nutrition* **6** 515, 1933.

11 Hirsch-Kauffmann, H., and Knauer, H. Ueber den Einfluss von Kohlehydrat- und Fettzufuhr auf Glykämie und Lipidstoffwechsel, *Med Klin* **29**:562 (April 21) 1933.

gave rise to a blood sugar curve similar to that produced by the administration of dextrose. On the contrary, Jacobsen,¹² Petré,¹³ Paasch and Schonfeld¹⁴ and Depisch and Hasenohrl¹⁵ have found that the ingestion of fat does not in the slightest influence the blood sugar level of normal persons during fasting. Schonfeld¹⁶ has even found that the administration of fat to children produces a reduction in the blood sugar level during fasting. Study of this subject in diabetes has been slight. Hirsch-Kauffmann and Knaue¹¹ found a rise in the blood sugar of diabetic children after the administration of 50 cc of olive oil. Paasch and Schonfeld¹⁴ in one case and Depisch and Hasenohrl¹⁵ in two cases found no change or the usual drop in sugar concentration which occurs in diabetic patients during the day while fasting.

Depisch and Hasenohrl¹⁵ have found further that the blood sugar curve for normal persons after the injection of insulin is not as low after the administration of fat as when no fat is given. They also found that the blood sugar curve for normal persons after the administration of dextrose is lower than when dextrose plus fat is given. They concluded that fat inhibits the action of both endogenous and exogenous insulin. Schur and his associates¹⁷ noted that the administration of insulin caused an increased deposition of fat after the feeding of fat to normal animals. They concluded that fat excites the secretion of insulin just as does carbohydrate, though to a lesser degree.

Joslin¹⁸ in his latest textbook has stated that insulin is concerned not only with the metabolism of dextrose but with that of protein and fat.

RATIONALE OF EXPERIMENTS

In this paper several experiments will be described which were performed for the purpose of determining the relationship between insulin and the metabolism of fat in diabetes mellitus. It is first necessary

12 Jacobsen, T. B. Untersuchungen über den Einfluss verschiedener Nahrungsmittel bei normalen, zuckerkranken und graviden, Personen, *Biochem. Ztschr.* **56** 471, 1913.

13 Petré, K. Studien über die Faktoren, welche bei gesunden Individuen und bei Diabetikern auf die Blutzuckercurve einen Einfluss ausüben, *Arch. f. exper. Path. u. Pharmacol.* **99** 52, 1923.

14 Paasch, G., and Schonfeld, H. Ueber den Ablauf der Blutzuckercurve nach Fettbelastung, *Monatschr. f. Kinderh.* **59** 181, 1934.

15 Depisch, F., and Hasenohrl, R. Weiterer Beitrag zur Blutzuckerregulation, Fett- und Kohlehydratstoffwechsel, *Klin. Wchnschr.* **8** 202 (Jan. 29) 1929.

16 Schonfeld, H. Zur Frage der Blutzuckerbeeinflussung durch perorale Fettzufuhr, *Monatschr. f. Kinderh.* **61** 432, 1935.

17 Schur, H., Low, A., and Krčma, A. Die Wirkung des Insulins auf die provisorische Unterbringung resorbierter Kohlehydrate und Fette im Organismus, *Wien. Arch. f. inn. Med.* **25** 203, 1934.

18 Joslin, E. P., Root, H. F., White, P., and Marble, A. *The Treatment of Diabetes Mellitus*, ed. 5, Philadelphia, Lea & Febiger, 1935, p. 17.

to take cognizance of the following points The metabolism of fat may be considered from two standpoints (1) deposition in tissues and (2) oxidation That there is no defect in the oxidation of fat even in the most severe stages of diabetes has been proved beyond doubt Insulin, therefore, is certainly not necessary for the oxidative metabolism of fat If it is at all concerned with the metabolism of fat, it would be only with its deposition in the tissues

The action of insulin, as contrasted with that of thyroid, is immediate in onset and lasts for only several hours Any action of insulin will make itself evident during this period Any phenomenon which makes its appearance several days or weeks later certainly cannot be ascribed to insulin

The pathologic physiology of diabetes mellitus is not understood in its entirety, but certainly one important factor is hypo-insulinism The administration of an excessive, definite dose of dextrose to a diabetic patient will engender the maximum secretion of insulin of which he is capable A blood sugar curve of a certain height and length will be obtained If a large amount of fat is given with the same dose of dextrose to the same patient, assuming that fat requires insulin for storage, less insulin would therefore be available for the metabolism of the dextrose, for when the dextrose is given alone the secretion of insulin is at its maximum It is logical, therefore, to assume that the blood sugar curve would be higher and the glycosuria more marked If, however, fat does not require insulin for its storage, then the curves for sugar in the blood and in the urine would be identical with those obtained when dextrose is given alone¹⁹

A study of the influence of fat on the blood sugar level of diabetic patients during fasting would be necessary in order to corroborate the aforementioned results It is logical to assume that if fat requires insulin for its utilization, a rise should occur, whereas if insulin is not concerned with the metabolism of fat the value would remain unchanged

The results obtained from a study of the influence of fat on the blood sugar level of normal persons during fasting are not necessary for our argument However, in view of the fact that there is a diversity of opinion on this subject, it was decided to include this work in our studies

METHOD OF PROCEDURE

GROUP 1 *Diabetic Patients Receiving Dextrose and Dextrose Plus Fat*—Experiments were performed on eleven diabetic patients To each of them 60 Gm

¹⁹ It has been shown (Wishnofsky, M, and Kane, A P Am J M Sc 189 545, 1935) that if equivalent amounts of dextrose and starch are given to a diabetic patient two days apart, the curves for the sugar contents of the blood and urine will be identical It is reasonable to assume that the same will hold true if equal quantities of dextrose are given two days apart

of dextrose in a 20 per cent aqueous solution was given in the morning after a fast of fourteen hours. Specimens of blood (venous) were taken at the fasting level, immediately before ingestion, one and one-half and three hours after the ingestion of the dextrose. The sugar content of the blood was determined by the Folin-Wu method. Urine was collected one and one-half, three and six hours after the ingestion of dextrose, and its sugar content was determined by the Benedict method.

Two days later, also in the morning after a fast of fourteen hours, 60 Gm of dextrose in a 20 per cent aqueous solution was given, immediately followed by 120 Gm of olive oil.²⁰ The specimen of blood was taken, and the urine was collected at the same periods as when dextrose alone was given. In the interval between tests the patients received their customary diets. Those who had been taking insulin continued to do so.

TABLE 1—*Concentration of Dextrose in Blood and Quantity of Dextrose in Urine of Diabetic Patients After Ingestion of Dextrose and of Dextrose and Olive Oil**

Case Number	Sugar, Mg per 100 Cc of Blood						Sugar, Gm per 100 Cc of Urine					
	Fasting Level		90 Min Post Cibum		3 Hr Post Cibum		0 to 90 Min Post Cibum		90 Min to 3 Hr Post Cibum		4 to 6 Hr Post Cibum	
	Dex trose	Dex trose and Fat	Dex trose	Dex trose and Fat	Dex trose	Dex trose and Fat	Dex trose	Dex trose and Fat	Dex trose	Dex trose and Fat	Dex trose	Dex trose and Fat
1	174	182	400	368	268	370	10.3	4.6	15.3	13.0	2.4	4.6
2	242	244	400	380	286	267	13.6	9.0	12.4	9.0	1.5	1.6
3	133	110	488	429	364	292	3.3	2.8	7.2	5.9	1.1	0.9
4	259	258	444	310	320	235	6.4	4.0	12.3	4.6	1.1	3.4
5	237	210	465	424	313	320	10.3	7.8	10.4	11.4	2.0	3.5
6	228	235	382	348	258	328	9.0	5.2			0.7	0.6
7	275	278	550	500	484	392	7.9	8.5	12.9	11.8	9.6	10.2
8	217	236	448	438	338	360	7.2	3.7	8.9	11.6	3.2	1.6
9	354	354	571	571	465	571	11.1	5.7	14.1	12.0	7.3	6.7
10	330	300	494	374	381	388	12.0	9.5	18.6	17.2	10.3	6.2
11	220	217	317	313	333	292	3.6	2.5	4.2	5.1	3.5	1.8
Average	243	239	451	405	348	347	8.6	5.75	11.7	10.15	3.88	3.72

* Sixty grams of dextrose and 60 Gm of dextrose plus 120 Gm of olive oil were ingested.

GROUP 2 *Diabetic Patients Receiving Fat Only*—Experiments were performed on thirteen diabetic patients. To each of them 120 Gm of olive oil was given in the morning after a fast of fourteen hours. Specimens of blood (venous) were taken at the fasting level immediately before the ingestion and one, two and three hours after the ingestion of olive oil. The sugar content of the blood was determined by the Folin-Wu method.

GROUP 3 *Normal Persons Receiving Fat Only*—Experiments were performed on ten normal persons. The procedure was identical with that for group 2.

ANALYSIS OF RESULTS

GROUP 1 *Diabetic Patients Receiving Dextrose and Dextrose Plus Fat*—In table 1 are recorded the concentrations of blood sugar and the amounts of dextrose in the urine after the ingestion of dextrose and

²⁰ Olive oil is 100 per cent fat.

after the ingestion of dextrose and fat. Statistical analysis²¹ reveals the following facts: 1. There is no significant difference in the concentrations of the blood sugar at the fasting level. 2. The concentration of the blood sugar is significantly greater one and one-half hours after the ingestion of dextrose than after the ingestion of dextrose and fat. This holds true also for the dextrose in the urine for ninety minutes post cibum. 3. There is no significant difference in the concentrations of dextrose in the blood three hours post cibum or in the dextrose in the urine from one and one-half to three hours and from four to six hours, inclusive, post cibum.

In a previous paper we²² stated our conclusion that fat does not influence the absorption of dextrose from the alimentary canal of human beings. The difference at the one and one-half hour level post cibum

TABLE 2—*Concentration of Dextrose in Blood of Diabetic Patients at Fasting Level and After Ingestion of 120 Gm of Olive Oil*

Case Number	Sugar, Mg per 100 Cc of Blood			
	Fasting Level	1 Hr Post Cibum	2 Hr Post Cibum	3 Hr Post Cibum
1	236	260	235	196
2	183	183	177	156
3	263	260	249	238
4	280	263	230	200
5	225	207	176	182
6	274	280	268	262
7	160	165	147	138
8	220	222	180	176
9	318	288	281	263
10	187	198	196	187
11	173	187	166	156
12	183	181	167	152
13	148	148	125	124

may be interpreted as an initial reduction in the rate of absorption of dextrose as a result of the retardation of the emptying of the stomach. For our purposes the important conclusion is that a large amount of fat does not increase the glycemia and glycosuria produced in diabetic patients by a definite dose of dextrose.

GROUP 2 Diabetic Patients Receiving Fat Only—In table 2 are recorded the concentrations of dextrose in the blood of thirteen diabetic patients at the fasting level and one, two and three hours after the ingestion of 120 Gm of olive oil. Vesa²³ has well described the drop in blood

21 The method of analysis used was that developed by R. A. Fisher (Statistical Methods for Research Workers, ed 3, London, Oliver & Boyd, 1930, p 104).

22 Wishnofsky, M., Kane, A. P., and Spitz, W. C. The Influence of Fat on the Absorption of Dextrose from the Human Alimentary Canal, *Am J Digest Dis & Nutrition* 4:174 (May) 1937.

23 Vesa, A. Studien über Diabetes mellitus unter Anwendung von zweistündlichen bei Tag und Nacht entnommenen Blutzucker- und Harnproben, *Acta med Scandinav*, supp 57, 1934, p 1.

sugar level which occurs during the day in fasting diabetic patients. This was noted in our patients and was in no way influenced by the ingestion of fat.

GROUP 3 Normal Persons Receiving Fat Only—In table 3 are recorded the concentrations of dextrose in the blood of ten normal persons at the fasting level and one, two and three hours after the ingestion of 120 Gm of olive oil. The concentration of dextrose is not influenced by the ingestion of fat.

COMMENT

In the review of the literature it was brought out that a strong impression exists that insulin is intimately concerned with the metabolism of fat. To recapitulate: 1. Allen has stated that insulin is either directly or in some secondary and indirect manner concerned with the metabolism

TABLE 3—*Concentration of Dextrose in Blood of Normal Persons at Fasting Level and After Ingestion of 120 Gm of Olive Oil*

Case Number	Sugar, Mg per 100 Cc of Blood			
	Fasting Level	1 Hr Post Cibum	2 Hr Post Cibum	3 Hr Post Cibum
1	107	90	84	86
2	122	105	103	100
3	93	95	91	95
4	90	86	93	95
5	90	87	90	
6	90	87	83	91
7	87	81	80	85
8	81	82	91	95
9	100	95	95	100
10	85	100	95	100

of fat. 2. Richardson has claimed that fat uses insulin for its own metabolism or in some way inhibits the use of insulin by carbohydrate. 3. Barach has stated that 1 Gm of fat creates the need for as much insulin as 2 Gm of carbohydrate. 4. Joslin has stated that insulin is just as much concerned with the metabolism of fat and protein as with that of carbohydrate. 5. Depisch and Hasenohil have stated as their conclusion that fat inhibits the action of both endogenous and exogenous insulin. 6. Schui and his associates have claimed that the administration of fat excites the secretion of insulin just as does carbohydrate, though to a lesser degree. 7. Himsworth has stated as his conclusion that fat retards and diminishes the action of insulin on the blood sugar.

It is important to reiterate that in the study of the relationship between insulin and the metabolism of fat the two following factors are of fundamental importance: 1. Insulin is not necessary for the oxidation of fat. It can be concerned, if at all, only with the deposition of fat in the tissues. 2. The action of insulin is immediate in onset and of

short duration. Any phenomena which appear days or weeks later cannot be ascribed to insulin.

A definite answer to this problem, namely, the influence of insulin on the metabolism of fat, can be obtained from the experiments herein described. Sixty grams of dextrose was given to each of a series of diabetic patients. The dextrose contents of the blood and urine were studied for a sufficiently long period, namely, six hours. The insulin response to this dose may be considered maximum. Two days later 60 Gm of dextrose was given with 120 Gm of fat. This amount of fat, given as a single dose, may be considered large. If fat required insulin for its storage it would make less insulin available for the metabolism of the dextrose, and a significant increase in the dextrose contents of the blood and urine should occur. But over a period of six hours this result did not occur. The important conclusion is that fat does not require insulin for its metabolism, for the same reason, it does not inhibit or retard the action of insulin. Allen¹ and Adlersberg and Poiges² have shown that the addition of considerable fat to a maintenance diet produces a depreciation of the tolerance of the diabetic patient for carbohydrate. This action makes its appearance only after days or weeks of increased feeding of fat. Their results are convincing. However, the mechanism producing this change must, in the present state of knowledge, be considered unknown.

The work on the influence of fat on the blood sugar level of diabetic patients during fasting has been fragmentary. We have studied this action in a series of thirteen diabetic patients and have found that a large dose of fat does not in the slightest prevent the fall in blood sugar level which occurs during the day in diabetic patients during fasting. The results do not have the critical value of those just described, they tend, however, to corroborate the conclusions drawn.

Large doses of fat do not influence the fasting level of the blood sugar of normal persons. This finding is in agreement with that of most investigators.

SUMMARY AND CONCLUSIONS

A review of the literature is given. A strong impression exists that insulin is intimately concerned with the metabolism of fat. Experiments are presented from which it is concluded that fat does not require insulin for its metabolism and that it does not inhibit or retard the action of insulin. Incidentally, it is shown that the ingestion of large amounts of fat does not influence the fasting level for blood sugar of diabetic patients or normal persons.

CHRONIC ARSENICAL POISONING DURING THE TREATMENT OF CHRONIC MYELOID LEUKEMIA

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The value of inorganic arsenical preparations in the treatment of chronic myeloid leukemia was neglected in the American medical literature from the time that roentgen therapy was suggested by Nicholas Senn¹ until the report of Forkner and Scott² in 1931. The 1931 report described a favorable reaction in nine of ten patients receiving solution of potassium arsenite in subtoxic amounts. Later Forkner³ described its successful use in eighteen patients, none of whom had received the drug for longer than one year. In 1936 Stephens and Lawrence⁴ reported on seven patients treated successfully for about four years or less. The early authors encountered no complications more serious than transient conjunctivitis, coryza, nausea and diarrhea. One patient had herpes zoster while taking arsenic, but the authors considered that this was as likely to be a feature of the leukemia as a result of the treatment. One of the patients exhibited generalized pigmentation of the skin after several months of arsenic medication, but no other complications were observed. All three papers by Forkner and Scott, and Stephens and Lawrence contained allusions to the possibility of more serious hepatic, renal or cutaneous lesions from prolonged ingestion of arsenic.

In this paper we wish to describe the course and necropsy observations in a case of chronic myeloid leukemia in which the patient was given intensive treatment with solution of potassium arsenite and roent-

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1 Senn, N. Case of Splenomedullary Leukaemia Successfully Treated by the Use of Rontgen Ray, *M Rec* **44** 281, 1903

2 Forkner, C E, and Scott, T F M. Arsenic as a Therapeutic Agent in Chronic Myelogenous Leukemia, *J A M A* **97** 3-5 (July 4) 1931

3 Forkner, C E. The Administration of Solution of Potassium Arsenite in the Treatment of Chronic Myelogenous Leukemia, *M Clin North America* **15** 1057-1064, 1932

4 Stephens, D J, and Lawrence, J S. The Therapeutic Effect of Solution of Potassium Arsenite in Chronic Myelogenous Leukemia, *Ann Int Med* **9** 1488-1502, 1936

gen therapy and in whom cutaneous and hepatic lesions due to the arsenic developed. Briefer notes on the results of arsenic therapy in five other patients with chronic myeloid leukemia who showed certain features of this form of treatment are included.

REPORT OF CASES

CASE 1—A 61 year old Jew, single, formerly a chauffeur, entered the University of Chicago Clinics on Aug 18, 1931. He had had a brownish blotchy discoloration of the skin of the trunk for about fifteen years. Two years prior to his admission to the clinic progressive enlargement of the lymph nodes, asthema, dyspnea, cough and epistaxis commenced. In the winter of 1930 a diagnosis of leukemia was made, the leukocyte count then was 64,000, and he was given twenty roentgen treatments, of unknown dosage, over the enlarged lymph nodes. This helped but little, and in August 1931 the leukocyte count was 24,000. One week before coming to the clinic he was given by a physician solution of potassium arsenite in increasing doses. On the day of registration the patient was taking 13 minims (0.8 cc) three times a day and was experiencing headache, nausea and vomiting for the first time. His past history and family history were irrelevant. His health and habits had been excellent.

Physical examination disclosed a thin, poorly nourished man with large, irregular brawny red blotches on the skin of the trunk and limbs. The heart was not enlarged. The blood pressure was 160 systolic and 90 diastolic. There was general arteriosclerosis of grade 2. The liver was palpable 15 cm below the right costal margin in the midclavicular line⁵, it was of normal consistency and tender. The spleen was relatively small and firm. It was easily felt protruding just below the left costal margin and was not tender. There was pitting edema of grade 2 of the legs from the groin downward. Varicosities were present on both legs. The prostate gland was enlarged and tender, and the expressed fluid contained much pus. All the superficial lymph nodes were enlarged, varying in size from that of a pea to that of a hazelnut. They were discrete, firm and non-tender. The Wassermann reaction of the blood was negative. Examination of the urine revealed no abnormality. The blood count showed hemoglobin, 11.5 Gm, erythrocytes, 4,200,000, and leukocytes, 7,600. The differential count showed myelocytes, 11 per cent, metamyelocytes, 4 per cent, polymorphonuclears, 68 per cent, lymphocytes, 12 per cent, monocytes, 4 per cent, and normoblasts, occasional.

The diagnosis was chronic myeloid leukemia, arteriosclerotic heart disease, with congestive heart failure of grade 2b, and chronic prostatitis.

Course—Chart 1 presents the variations in the leukocyte count, the doses of solution of potassium arsenite and the dates of the roentgen treatments. Throughout the entire illness the hemoglobin value and the red cell count were easily maintained at a good level with occasional courses of iron medication. The leukocyte count was kept at reasonable levels by the persistent administration of solution of potassium arsenite, as indicated. Nevertheless, the course was not satisfactory, because of the persistent congestive heart failure, which in the last year of life was characterized by paroxysmal dyspnea at night and on exertion.

⁵ All estimations of the enlargement of the liver or spleen were made by measuring from the lower border of the ribs in the midclavicular line of the side involved.

Electrocardiograms displayed a low T wave, a slurred QRS complex and a shifting pacemaker. Roentgenograms at different times showed first a normal chest with a normal-sized heart, and, later, fine granular infiltration of the pulmonary fields and signs of pulmonary congestion.

In 1935 osteoporosis of the ribs was demonstrated. In December 1935 230 roentgens of radiation was given over the painfully enlarged cervical lymph nodes. This was the first roentgen therapy that was given after the patient came under our care in 1931.

On July 23, 1936, the patient was hospitalized because of severe cardiac asthma, rectal bleeding and profound weakness. At this time he complained of tenderness of the soles. The cardiac symptoms improved rapidly with rest in bed and appropriate medication. The melena was found to be due to a polyp or a leukemic infiltration. This was treated satisfactorily with 780 roentgens of radiation to the perineum. When admitted to the hospital the patient had taken no solution of potassium arsenite for about six weeks, and the leukocyte count was 80,000. After ten days of treatment with this drug in doses of 10 to 21 minims (0.6 to

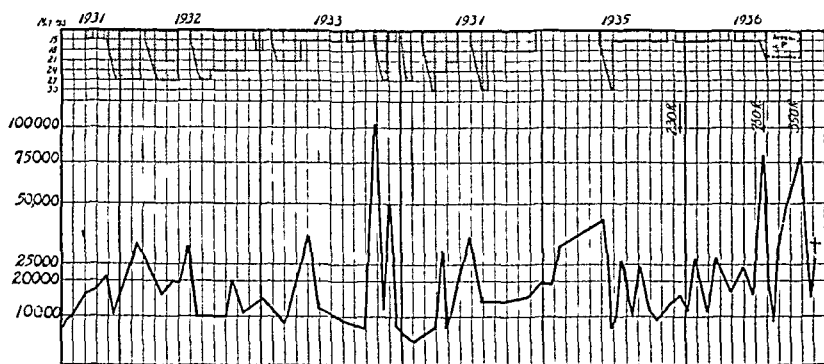


Chart 1 (case 1) —The leukocyte counts and the total daily doses of solution of potassium arsenite in minims

1.3 cc) daily, the leukocyte count declined to from 15,000 to 20,000. At this time the dermatologist diagnosed the painful condition of the feet as arsenical hyperkeratosis and advised the use of a less toxic preparation—pills containing arsenic trioxide. The pills prepared in the clinic contain 9 mg of arsenic trioxide. Two of these were given daily until the patient was discharged. After that he took 4 pills weekly until his final admission to the hospital. When he entered the hospital on July 23, 1936, glycosuria was discovered for the first time, although specimens of urine had been examined frequently in the outpatient department. This amounted to 2 Gm in the twenty-four hour specimen. The value for blood sugar during fasting was 205 mg per hundred cubic centimeters. With a diet containing 120 Gm of carbohydrate, 50 Gm of protein and 90 Gm of fat, the glycosuria stopped, and the value for blood sugar decreased to 110 mg. The diet was then increased to 180 Gm of carbohydrate and later to 230 Gm of carbohydrate, 65 Gm of protein and 90 Gm of fat, with no return of the glycosuria. The patient was discharged on August 5 in fair condition.

He was readmitted for three days on August 18 because of severe paroxysmal dyspnea provoked by the hot weather. When he left the hospital he entered a convalescent home, where no examinations of the blood or urine were made. On November 6 he returned to the hospital because of severe cardiac asthma. The leukocyte count was 33,600, and because of his poor general condition the

patient was given no more arsenic. He received about 350 roentgens of radiation to the inguinal and mediastinal lymph nodes, which brought the leukocyte count down to 13,500. The first twenty-four hour specimen of urine contained 142 Gm of sugar, and during fasting the value for blood sugar was 259 mg and that for cholesterol was 165 mg. With a diet of 150 Gm of carbohydrate, 70 Gm of protein and 150 Gm of fat for seven days, the urinary value for sugar declined to 43 Gm. The diet was then changed to 100 Gm of carbohydrate, 60 Gm of protein and 150 Gm of fat. Values of from 12 to 15 Gm of sugar in the urine persisted, and the blood sugar value during fasting remained at 255 mg. The diet was then increased to 200 Gm of carbohydrate, 60 Gm of protein and 100 Gm of fat, and insulin was given. Surprisingly small amounts of insulin were required: 35, 20, 20, 10, 15, 10, 15 units, respectively, on consecutive days. With this regimen the blood sugar value during fasting changed to 171 mg and the urinary value for sugar decreased to 25 Gm in twenty-four hours. The patient died rather suddenly of heart failure on December 2, approximately seven years after the onset of leukemia.

Gross Postmortem Examination (by Dr. Paul R. Cannon).—The skin was brown, dry and apparently keratotic over the abdomen. The soles of the feet were unusually thick and scaly, particularly over the heels, and there was a small fleshy wart on the small toe of the left foot. The cervical, axillary and inguinal lymph nodes were moderately enlarged.

The right side of the pleural cavity contained no fluid, the left was obliterated by fibrous adhesions. The left lung was vascular, and the parenchyma was friable in the posterior portion. The right lung was edematous. The bronchi were thick walled and contained no pus. The pericardial cavity contained no fluid. The heart weighed 310 Gm, and the right chambers were distended. The right auricle was filled by a lobular mass of cream-colored blood clot, slightly mottled externally by red but on the cut surfaces pearly throughout. Similar white clots were present in the right ventricle and the pulmonary artery. On the left the myocardium averaged from 15 to 17 mm in thickness and contained anteriorly a firm fibrous patch, measuring 1.5 by 1 cm. There were small fibrous patches in the form of linear streaks throughout the myocardium. The coronary arteries were calcified, particularly the anterior descending branch on the left. The aorta showed marked atheroma and calcification.

The liver weighed 1,950 Gm and the capsular surface was somewhat nodular. The organ cut with increased resistance and presented a surface made up of lobules varying from 2 to 10 mm in diameter. Some were whitish, and all were separated by an increased amount of fibrous tissue. The spleen weighed 515 Gm and was covered by fibrous adhesions which bound it to the lateral peritoneal wall and to the stomach. The capsule laterally was an opaque tissue 1 cm thick in places. The organ cut with increased resistance, and its surfaces were of an unusual (almost rocklike) hardness. It consisted mainly of increased fibrous trabeculae, with intervening portions of grayish red tissue. The pancreas was small, firm and fibrous. There was moderate epithelioidosis of the esophagus. The gastric mucosa had a distinctly mamillated appearance, the nodules having a diameter of from 2 to 5 mm. There were many submucous hemorrhages in the colon and some erosions. The lower portion of the rectum showed no leukemic nodules or polyps. The kidneys were normal, except for one leukemic mass in the pelvis, measuring 15 by 7 mm.

A portion of the liver was given to the coroner's chemist for analysis. It contained 62.5 mg of arsenic per hundred grams of tissue.

Histologic Postmortem Examination (by Dr Cannon) —“The sinusoids and portal areas (of the liver) are diffusely infiltrated with myeloid cells, the majority of which are mature polymorphonuclear leukocytes, although occasional myelocytes may be seen. There are no definite leukemic nodules. Mallory stains for connective tissue show a definite portal cirrhosis in a moderately early stage. The hepatic cells are not fatty and do not contain hemosiderin in unusual amounts. There is considerable regeneration of hepatic cells. The gallbladder is normal. Fatty changes are minimal.

“The capsule and trabeculae of the spleen are greatly thickened and hyalinized and the trabeculae contain occasional areas of hemosiderin deposit. The malpighian bodies are absent, and the red pulp is scanty and largely infiltrated by leukocytes and myelocytes, with a diffuse increase in fibrous tissue.

“The pancreas contains a great increase in interstitial as well as intralobular connective tissue. Round cells and myeloid elements are present in this connective tissue. Islet tissue is inconspicuous but in places shows a definite increase in connective tissue. The smaller arteries and arterioles are thick walled. There is no hemosiderin.

“The bone marrow shows marked hyperplasia, immature myeloid elements and some absorption of trabeculae. There are occasional areas of fibrous replacement of bone marrow.

“The myocardium shows considerable diffuse and focal myofibrosis, with occasional accumulations of leukemic cells. Lipochrome pigmentation shows only in stains for fat.

“The skin of the sole of the foot shows marked hyperkeratosis, with absence of pigmentation of the stratum germinativum and of inflammation of the corium. The skin of the body shows less marked hyperkeratosis but exhibits hemosiderin-filled macrophages scattered through the corium.

“The plicae of the stomach are prominent, and the mucosa is densely infiltrated by leukemic cells.

“The tracheobronchial and abdominal lymph nodes are hyperplastic and densely infiltrated by leukemic cells.

“The leukemic clot from the heart consists almost entirely of leukemic cells in various stages of maturation and fibrin, with few red corpuscles.”

Comment —This patient's leukemic blood picture was well controlled with solution of potassium arsenite alone for four and a half years. Roentgen irradiation was given to the clavicular region for painfully enlarged lymph nodes, to the perineal region for a rectal polyp or leukemic infiltration, to the inguinal nodes because of tenderness and enlargement and to the mediastinal region because of cough. The spleen, the traditional recipient of roentgen therapy, was given none. Pills containing arsenic trioxide were given in doses calculated to supply as much arsenoxide as the usual dose of solution of potassium arsenite did not keep the leukocyte count down (chart 1), whereas the last roentgen therapy to the inguinal region promptly reduced the count. The terminal diabetic episode was peculiar, and the easy control with a diet rich in carbohydrate and small amounts of insulin is of interest. Joslin's series of diabetic patients includes only one (case 7260) with myeloid leukemia. Hemochromatosis, which is superficially like the con-

dition in the present case, is also accompanied with cirrhosis of the liver, but the patient requires large amounts of insulin. In Joslin's textbook there is nothing to guide one in deciding whether the cirrhosis, the arsenic, the fibrosed pancreas or destiny induced this patient's diabetes. There is no proof that the portal cirrhosis was due to arsenic, but with regard to the high arsenic content of the liver and the general recognition of arsenic as a possible etiologic agent, it seems most likely. At no time during his illness did this patient have herpes zoster or any definite neuritic pain.

CASE 2—The patient, a 56 year old American man, was first seen at the University of Chicago Clinics on Sept 22, 1933. He complained of fatigue, dyspnea, cough and pain in the left upper portion of the abdomen of two years'

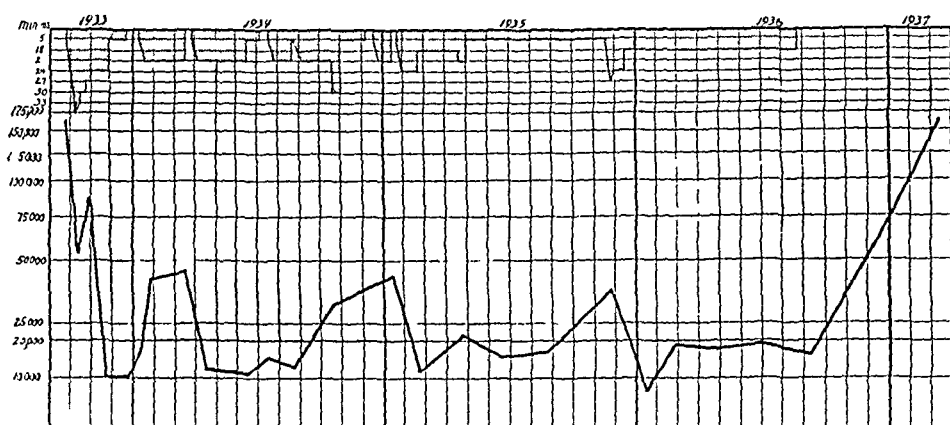


Chart 2 (case 2) —The leukocyte counts and the daily doses of solution of potassium arsenite

duration and of increasing severity. He was married and had two healthy children. He had always been well and was of moderate habits.

Physical examination revealed moderate enlargement of the lymph nodes generally. The spleen, which was somewhat tender, filled the left iliac region and extended downward to the umbilicus. The Wassermann reaction of the blood was negative, and the urine was normal.

A blood count showed hemoglobin, 7.8 Gm, erythrocytes, 2,460,000, and leukocytes, 164,800. The differential count showed myeloblasts, 11 per cent, promyelocytes, 19 per cent, myelocytes, 3 per cent, metamyelocytes, 1 per cent, polymorphonuclears, 51 per cent, monocytes, 10 per cent, lymphocytes, 4 per cent, and normoblasts, 15 per hundred leukocytes. The stained films of the blood were distinctive because of the many mitotic figures in the erythroblasts and occasionally in the myelocytes.

Course—Five minims (0.3 cc) of solution of potassium arsenite three times a day was ordered, the dose to be increased by 1 minim (0.06 cc) daily until unpleasant symptoms resulted. The data on the leukocyte counts and the doses of arsenic are shown in chart 2. At the onset of treatment and at intervals thereafter iron was given, and the hemoglobin value and red corpuscle count were easily kept at high levels. Three months after treatment with solution of potassium arsenite was started the patient had generalized erythema for one day.

In April 1934, eight months after coming under our care, the patient showed his maximum weight, and one examiner described finding a small amount of free fluid in the abdomen. On his next visit to the clinic the patient said he felt much better, he weighed 2 Kg less and there was no sign of a fluid wave. After that the only difficulty he encountered was with fairly severe bronchitis in cold damp weather. In spite of this he was able to conduct his business and go hunting, and he felt fairly well. In August 1936 he yielded to a friend's enthusiasm for chiropractic treatments and stopped taking solution of potassium arsenite in September. The leukocyte count in August was 17,000, and the spleen extended 2 or 3 cm below the left costal margin. The patient returned to the clinic, repentant, with a leukocyte count of 163,000 and with the spleen palpable 9 cm below the left costal margin. The arsenic therapy was resumed.⁵¹

Comment—From a cytologic point of view this patient's leukemia seemed severe, with many primitive cells and many mitoses, but the course with solution of potassium arsenite has been satisfactory. He took the drug almost continuously until his recent defection. It seems certain that this man had arsenical hepatitis at the time that ascites was detected. No lesions of any sort have appeared on the skin, and it is with great interest that we anticipate continuance of the arsenic regimen.

CASE 3—The patient, a 30 year old American business man, was referred to the University of Chicago Clinics on Jan 25, 1930, with the diagnosis of chronic myeloid leukemia. He had had headaches and fatigue during the previous year and pain in the left upper portion of the abdomen of two weeks' duration. He was a widower, his past history and family history were noncontributory.

Physical examination revealed gross enlargement of the spleen, which caused the abdomen to protrude. The viscus was firm and tender and extended to within 2 cm of the symphysis pubis and just across the midline. The liver was felt 3 cm below the right costal margin. There was no enlargement of the lymph nodes. The Wassermann reaction of the blood was negative. Examination of the urine did not reveal any abnormality. A blood count showed hemoglobin, 11 Gm, erythrocytes, 3,620,000, and leukocytes 535,000. The differential count showed myelocytes and metamyelocytes, 44 per cent, polymorphonuclears, 45 per cent, eosinophilic myelocytes and polymorphonuclears, 10 per cent, and normoblasts, 4 per hundred leukocytes. The basal metabolic rate was plus 41 per cent.

Course—The patient was given a series of nine roentgen treatments in fifteen days over the long bones and the spleen. The total dose was about 1,800 roentgens. After this series the leukocytes numbered 167,000, the basal metabolic rate was plus 10 per cent and the stained film contained fewer myelocytes. On February 8 the leukocyte count was 12,100, and the spleen was palpable only 8 cm below the left costal margin. The leukocytes numbered 6,200 on April 5. The patient received no treatment of any sort until May 1931, when he was hospitalized again because of a sudden increase in the leukocyte count. He received five roentgen treatments, totaling about 950 roentgens, over the long bones and the thoracic portion of the spine. The leukocyte count (chart 3) decreased from 73,000 to 14,600 after the fifth treatment. In June 1931 solution of potassium arsenite was

5a In June 1937, after this paper was written, the patient's leukocyte count was 12,900, and he was back at work.

prescribed. It was taken by the patient in twenty-one day cycles, starting with 5 minims (0.3 cc) three times a day and increasing the dose 1 minim (0.06 cc) daily until a dose of 9 minims (0.55 cc) three times a day was reached. After the twenty-first day the treatment was stopped, the patient rested for three weeks and then began all over again. The usual result was a variation of the leukocyte count between about 40,000 and 6,000. In December 1931 herpes zoster developed and a month later, when the patient was seen at the clinic, he was in excellent condition. The spleen was barely palpable. The blood count showed hemoglobin, 16.6 Gm, erythrocytes, 4,790,000, and leukocytes, 63,300. The differential count was promyelocytes, 2 per cent, myelocytes, 6 per cent, metamyelocytes, 8 per cent, polymorphonuclears, 69 per cent, basophils, 5 per cent, eosinophils, 1 per cent, lymphocytes, 6 per cent, and normoblasts, 0.

The patient continued with the solution of potassium arsenite and was able to keep the leukocyte count almost within normal limits, but resting from the use

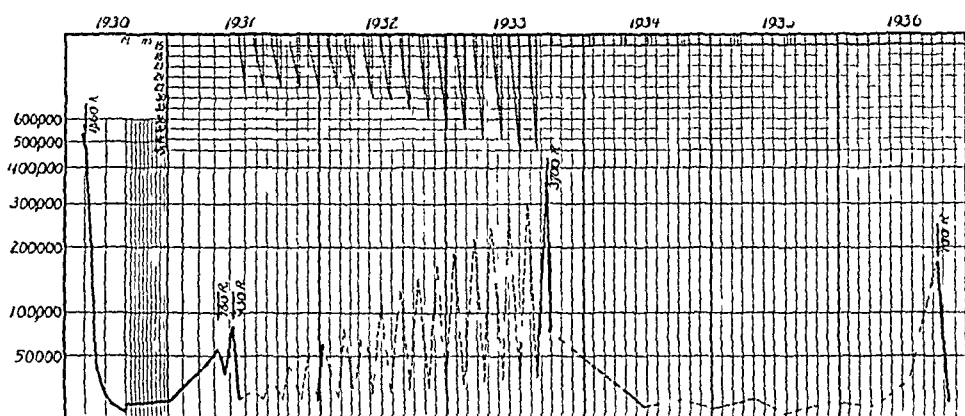


Chart 3 (case 3) —The leukocyte counts and the daily doses of solution of potassium arsenite

of the drug would be followed by an increase to over 100,000 in three weeks. He returned to the clinic in September 1933 because he felt poorly. He told of having numbness of the legs and an ataxic gait, which improved when the arsenic was stopped. At this time the leukocytes numbered 340,000. He was given another series of roentgen treatments, 3,700 roentgens to the spleen and long bones over a period of eleven days. When he left after this treatment the leukocyte count was 73,000. During the next year he took about 15 minims (0.9 cc) of solution of potassium arsenite daily, stopping for three weeks whenever the leukocyte count was less than 6,000. He was last seen by us in June 1934, when the leukocyte count was 11,000, the spleen was palpable only on inspiration, and his condition was satisfactory. Contact with this patient has been maintained by correspondence. In October 1936 the leukocyte count was 180,000, and he received 800 roentgens of radiation at the Harper Hospital in Detroit. On Nov 10, 1936, the leukocytes numbered 10,200 and the erythrocytes, 4,300,000, and the hemoglobin value was 85 per cent. Since 1934 he has taken solution of potassium arsenite regularly and in general according to the scheme previously mentioned.

Comment —This case illustrates the possibilities of benefit in thoroughly controlled cases of chronic myeloid leukemia. The man is intelligent and has had a leukocyte count made weekly for years. Throughout the seven year course of the disease he has attended to his business,

traveled and remarried and until recently has been healthy. The only evidence of arsenic intoxication that he has shown, aside from nausea, has been the herpes zoster and the neuritis, which occurred early and disappeared.

CASE 4—A 45 year old housewife entered the Billings Hospital on April 27, 1931. She complained of severe pain in the left upper portion of the abdomen of one day's duration and easy fatigue and weakness throughout the preceding year. Six months before she came to the clinic she was told that her spleen was enlarged, and she was given a diet and diathermy treatments. Her health had always been good. She had had two children and no miscarriages. The menses were regular and not excessive.

On physical examination there were marked pallor and minor enlargement of all the lymph nodes. The abdomen protruded, and the spleen, which filled the left iliac region and extended 10 cm. below the left costal margin, was tender. Exam-

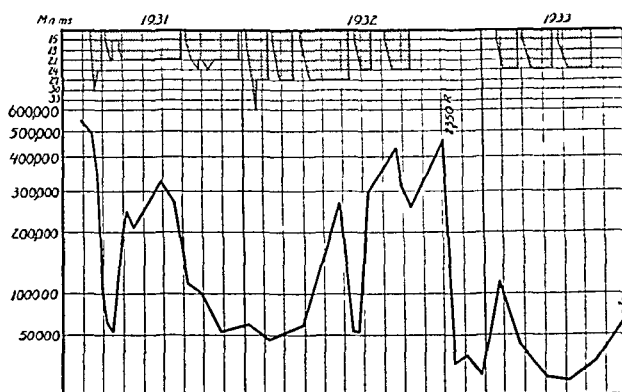


Chart 4 (case 4) —The leukocyte counts and the daily doses of solution of potassium arsenite

nation of the urine did not reveal any abnormality. The Wassermann reaction of the blood was negative. The blood count showed hemoglobin, 8.5 Gm., erythrocytes, 2,600,000, and leukocytes, 570,000. The differential count was myelocytes, 16 per cent, basophilic myelocytes, 8 per cent, metamyelocytes, 20 per cent, polymorphonuclears, 52 per cent, eosinophils, 3 per cent, and basophils, 1 per cent.

A diagnosis of chronic myeloid leukemia and acute perisplenitis was made. Two days later a friction rub was heard over the spleen, and in the course of ten or twelve days the perisplenitis subsided.

Course—While this patient was in the hospital, solution of potassium arsenite was given in the usual manner. Chart 4 shows graphically the excellent response to this treatment. For one year her condition was fair, but the white cell count never reached normal levels, and the anemia did not improve strikingly. The spleen decreased somewhat in size, so that the right border receded to the left of the midline. In the summer of 1932 the spleen increased in size, and the leukocyte count steadily rose. The patient tolerated the arsenic poorly, and by August 1932 could take only 21 minims (13 cc.) daily without provoking nausea and diarrhea. She suffered intensely from the heat and was hospitalized for a week in August. At that time the hemoglobin value was 9.2 Gm., the erythrocyte

count, 3,200,000, and the leukocyte count, 368,000. During the next two months she grew steadily worse, and on November 2 she returned to the hospital for roentgen therapy. At this time examination of the blood showed hemoglobin, 8 Gm, erythrocytes, 2,800,000, and leukocytes, 450,000. She was given 2,340 roentgens over the spleen in the course of twelve days, and on the day of her discharge, November 16, the leukocytes numbered 22,000. The size of the spleen diminished after this until it extended only to the umbilicus. The patient felt fairly well until June 1933, when she became anemic, weak and feverish. She entered the hospital on July 26. The blood count was hemoglobin, 4.8 Gm, erythrocytes, 2,000,000, and leukocytes, 64,000. The spleen was tender and filled the entire left side of the abdomen. The patient became rapidly worse and died on August 3 of bronchopneumonia.

Comment—At autopsy the spleen weighed 2,900 Gm and the liver 2,700 Gm. The histologic appearance of the spleen and the bone marrow was typical of myeloid leukemia. This case illustrates the action of solution of potassium arsenite in the more severe type of leukemia. Certainly the initial response was excellent, but one wonders if the patient's inability to tolerate the large doses of arsenic or some inherent difference in the disease accounts for the unsatisfactory course as compared with that of the third patient. Great difficulty was experienced in attempting to keep this patient's hemoglobin value at a safely high level. No complications of the arsenical therapy except gastro-intestinal disturbances occurred.

CASE 5—A 28 year old housewife of Italian parentage was first seen at the University of Chicago Clinics on Jan 12, 1931, seeking further treatment of a condition diagnosed elsewhere as lymphatic leukemia. She related that she had been perfectly well until she became pregnant in February 1930. Throughout gestation she suffered continuously from headaches, pain in the back, nausea and vomiting. On November 19, under the care of a midwife, she was delivered precipitously of a normal 6 pound (2,722 Gm) girl. Delivery was followed by severe post-partum hemorrhage. The physician who was called controlled the hemorrhage and discovered an enlarged spleen. Three weeks later the patient was taken to the Burnside Hospital and given approximately four-tenths of an erythema dose of roentgen therapy. This reduced the leukocyte count from 188,000 to 132,000.

Examination at the clinic showed an enlarged spleen, which extended to the midline from the xiphoid to the umbilicus, filled the left iliac region and extended 16 cm below the left costal margin. It was firm and smooth but not tender. There was no enlargement of any of the palpable lymph nodes. The Wassermann reaction of the blood was negative. Examination of the urine did not reveal any abnormality. The blood count showed hemoglobin, 12.5 Gm, erythrocytes, 3,670,000, and leukocytes, 195,000. The differential count was myelocytes, 3 per cent, metamyelocytes, 9 per cent, polymorphonuclears, 56 per cent, monocytes, 11 per cent, lymphocytes, 10 per cent, eosinophils, 2 per cent, and basophils, 3 per cent.

The diagnosis was chronic myeloid leukemia.

Course—When first seen the patient was having considerable intestinal distress, so administration of solution of potassium arsenite was delayed, and only iron

was given to improve the red cell count. The leukocyte count increased to 388,000 in March. From March 26 to April 10 she was given 700 roentgens of radiation over the spleen. As a result the leukocyte count fell to 86,000. When it began to increase in June 1931, solution of potassium arsenite was prescribed. Chart 5 shows graphically the course of the leukocyte counts and the doses of the drug. During the succeeding year the patient was in good health except for troublesome chronic bronchitis during the winter. In June 1932 the soles were sore, and the dermatologists made a diagnosis of arsenical (?) keratosis. At about the same time the patient began to tolerate arsenic less well, and on October 5 she entered the hospital for more irradiation. The examination of the blood showed hemoglobin, 13 Gm., erythrocytes, 3,450,000, and leukocytes, 167,000. The differential count was myeloblasts, 9 per cent, promyelocytes, 4 per cent, myelocytes, 7 per cent, metamyelocytes, 1 per cent, polymorphonuclears, 60 per cent, eosinophils, 2 per cent, basophils, 8 per cent, monocytes, 4 per cent, lymphocytes, 4 per cent, and normoblasts, 8 per hundred leukocytes.

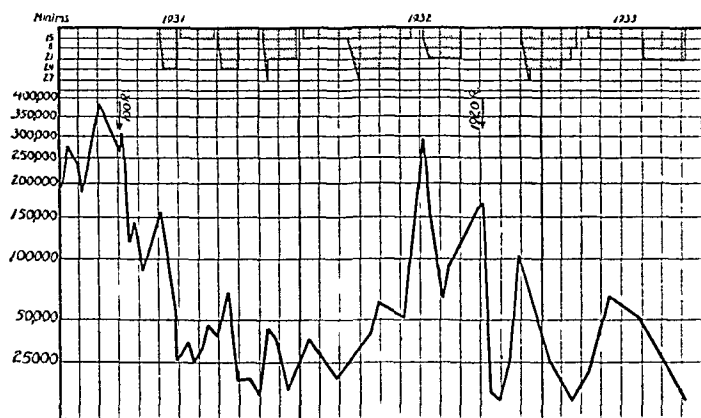


Chart 5 (case 5) —The leukocyte counts and the daily doses of solution of potassium arsenite

The spleen, which had become decreased in size after the first series of roentgen treatments, almost filled the entire left side of the abdomen, but it was not tender. In eight days the patient was given 1,900 roentgens of radiation over the spleen. When the patient was discharged, on October 14, the leukocytes numbered 15,000. By taking solution of potassium arsenite in small doses almost continuously, the patient kept the count low, but her general condition was poor. She was last seen by us in November 1933 and since then has been under the care of other physicians. The course after she left the clinic is unknown to us.

Comment —This case is interesting because the patient went through pregnancy and parturition in the early stage of leukemia. The response to therapy with solution of potassium arsenite so soon after a course of roentgen therapy is instructive, since it suggests that arsenic may be given as soon after roentgen therapy as the leukocyte curve ceases to fall. The keratosis which this patient had was mild and appears to have regressed, for after the time the diagnosis was made while her feet were being examined for fungi there is no further mention of foot trouble.

CASE 6—A 40 year old Slovakian man came to the University of Chicago Clinics on Oct 9, 1931. He related that suddenly two years previously he felt severe pain in the left upper portion of the abdomen. He had to remain in bed and consulted many physicians. Finally in the fall of 1929 a diagnosis of myeloid leukemia was made, and he was given thirty-five roentgen treatments. The spleen, which had been "enormous," decreased in size, and the patient was able to return to work. In the summer of 1931 the spleen enlarged again, and the patient received fifteen more roentgen treatments just before registration at the clinic. His past and his family history were irrelevant, he had always been robust until the present illness.

Examination showed roentgen pigmentation of the skin of the abdomen. The spleen protruded and was felt 3 cm. to the right of the midline and 17 cm. below the left costal border. There was no friction rub, and the viscus was firm and not tender. The Wassermann reaction of the blood was negative. Examination of

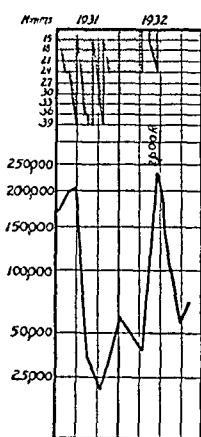


Chart 6 (case 6)—The leukocyte counts and the daily doses of solution of potassium arsenite

the urine did not reveal any abnormality. The blood count showed hemoglobin, 11.2 Gm., erythrocytes, 3,770,000, and leukocytes, 163,200. The differential count was myeloblasts, 2 per cent, promyelocytes, 2 per cent, myelocytes, 8 per cent, eosinophilic myelocytes, 1 per cent, metamyelocytes, 21 per cent, polymorphonuclears, 55 per cent, eosinophils, 2 per cent, basophils, 4 per cent, monocytes, 1 per cent, lymphocytes, 4 per cent, and normoblasts, 3 per hundred leukocytes.

Course—The patient was given solution of potassium arsenite in the usual manner but had to consume large amounts before the leukocyte count decreased. Chart 6 gives a graphic representation of the leukocyte counts and the doses of arsenic. The patient was well until January 1932, when herpes zoster developed. In February he complained of breathlessness and weakness and asked for more roentgen therapy. On February 26, after no solution of potassium arsenite had been taken for two weeks, the leukocytes numbered 232,000. From then until March 28 he received 2,650 roentgens of radiation over the spleen and the long bones. At that time the leukocyte count was 64,000. The differential count was myeloblasts, 5 per cent, promyelocytes, 7 per cent, myelocytes, 1 per cent, eosinophilic myelocytes, 2 per cent, basophilic myelocytes, 2 per cent, metamyelo-

cytes, 6 per cent, polymorphonuclears, 57 per cent, basophils, 8 per cent, lymphocytes, 8 per cent, monocytes, 8 per cent, and normoblasts, 5 per hundred leukocytes

After this the patient disappeared and could not be traced by our follow-up letters

Comment—This is another case in which herpes zoster developed in the course of treatment with solution of potassium arsenite. It is of interest, too, because it illustrates how refractory some patients may be to the drug. But it is to be noted that persistence in increasing the dose produced the desired, if only temporary, result.

COMMENT

The development of arsenical keratosis, arsenical cirrhosis or arsenical neuritis as a consequence of the therapeutic use of arsenic depends on the form of the drug employed, the duration of its administration and a special susceptibility of the patient. The form of arsenic used for our patients is arsenous trioxide, or arsenoxide, a white crystalline powder. Its highly poisonous properties have been known since the Christian era, and as a chief constituent of "aqua Tofana" (a solution containing arsenic) it was well known in the fifteenth and sixteenth centuries. Solid arsenoxide is used therapeutically chiefly in the "Asiatic pill" (7 mg per dose), but, as was shown in the description of case 1, it is less effective than are solutions. Dry white arsenic is poorly absorbed from the intestinal tract, and the smallest single fatal dose recorded by Witthaus⁶ was 2 Gm. Solutions of white arsenic were prepared early, and as "tasteless ague drops" they were a popular medicine in England prior to the general use of quinine for malaria. A Dr. Thomas Fowler, of Stafford, England, developed a preparation of arsenoxide, potassium carbonate and tincture of lavender, which was described in "The Edinburgh New Dispensatory"⁷ for 1794. This recipe contained about 1 per cent of arsenous trioxide and is still used with unchanged proportions as liquor arsenicalis B. P., or solution of potassium arsenite U. S. P. (more commonly called Fowler's solution). The preparation is poisonous, and 15 cc taken in "broken doses in four days"⁸ has caused death. This amount is equivalent to 150 mg of arsenoxide. In therapeutic practice the ordinary dose ranges from 0.6 to 2 cc per day (9 to 30 minims) in divided doses and represents from 6 to 20 mg

6 Witthaus, R. A., and Becker, T. C. *Medical Jurisprudence, Forensic Medicine and Toxicology*, ed 2, Baltimore, William Wood & Company, 1911, vol 4, p 439.

7 Duncan, A. *The Edinburgh New Dispensatory*, ed 4, Philadelphia: T. Dobson, 1794, p 102.

8 Peterson, F., Haines, W. S., and Webster, R. W. *Legal Medicine and Toxicology*, ed 2, Philadelphia, W. B. Saunders Company, 1923, vol 2, p 207.

of arsenoxide Stockman,⁹ in a report of a case of arsenical cirrhosis associated with the taking of liquor arsenicalis, stated that when this drug was given to children with chorea in the usual doses, pigmentation of the skin occurred after the administration of 17,900, 9,450, 12,600, 1,050, 360, 3,000, 260, 450, 12,000, 1,950 and 690 mg of arsenic, respectively. He quoted Gowers as saying that the smallest amount of arsenic which he had ever known to give rise to pronounced arsenical pigmentation was equivalent to about 11,000 minims (7,300 mg of arsenic) of liquor arsenicalis during two years. Gowers' usual dose was 0.3 cc three times a day. More recently Halter¹⁰ studied the effect of arsenous trioxide injected intramuscularly daily into patients with dermatologic conditions. He considered a decrease in the leukocyte count to about 4,000 as evidence of intoxication. The drug was given in amounts, increased daily, of from 2 to 10 mg. In thirteen of twenty-six patients with psoriasis so treated leukopenia developed. Seven of these showed other signs of intoxication. When leukopenia occurred, these patients had received 185, 48, 232, 134, 100, 215 and 155 mg of arsenoxide, respectively. In eight of a group of fifteen patients with other dermatoses leukopenia developed. No patient received more than 280 mg in a course of treatment, one patient was given three courses, and the leukocyte count reached 4,000, 5,000 and 4,300 after 185, 136 and 280 mg of arsenic, respectively. The lowest count was seen in a 4 year old child whose leukocytes numbered 2,100 after 135 mg of arsenoxide had been given. Delépine,¹¹ who performed experiments on rats as a part of the investigation of the Manchester outbreak of arsenical poisoning in beer drinkers, concluded that a dose "of $\frac{1}{150}$ to $\frac{1}{25}$ gram daily is capable of producing injurious effects in the ill-fed or weak individuals." The beer which was responsible for this epidemic was estimated to contain from 10 to 60 mg of arsenoxide per gallon, and the victims, mostly heavy drinkers, probably consumed from 5 to 30 mg of arsenoxide daily.

Toxicologically this marked variation in susceptibility to arsenic intoxication is important, and it is unfortunate that so few competent analyses are reported of the arsenic content of the viscera of persons receiving large amounts therapeutically. Several analyses after acute poisoning have been recorded, but these are of interest chiefly to the criminologist. It is generally accepted that absorbable forms of arsenic are eliminated solely by the kidneys, although small quantities are

9 Stockman, R. Chronic Arsenic Poisoning, *Edinburgh M J* **27** 1-10, 1921.

10 Halter, K. Untersuchungen über die Leukocytenzahl bei Darreichung anorganischen Arsens, *Klin Wchnschr* **15** 52-54 (Jan 11) 1936.

11 Delépine, in Report of the Royal Commission on Arsenical Poisoning, London, His Majesty's Stationery Office, 1903, vol 1, appendix 16, p 185.

deposited in the bones, the skin and the hair Dutcher and Steel¹² gave a dog 35 mg of arsenic and recovered 71 per cent from the urine in the next twenty days Scolosuboff¹³ fed a dog from 5 to 15 mg of sodium arsenite daily for thirty-four days The dog was killed, and the analysis disclosed the following values for arsenic 0.25 mg per hundred grams of muscle, 2.71 mg per hundred grams of liver, 8.85 mg per hundred grams of brain and 9.33 mg per hundred grams of spinal cord

McNally¹⁴ quoted from a thesis of Garnier¹⁵ in which it was reported that in two patients who died of tuberculosis while under treatment with solution of potassium arsenite U S P the brain contained more arsenic than did the liver In the Royal Commission's investigation¹¹ of the Manchester epidemic, arsenic was sought in the viscera, i e., liver, spleen and intestines hashed together, and in one instance there was found "0.011 grain in 13½ ounces" In three other cases in which death had taken place fourteen, thirty-two and fifty-two days, respectively, after beer was no longer taken, arsenic was detected in the viscera but was present in amounts too small to be weighed In one case, that of a woman who presented marked symptoms of arsenical poisoning during life and who died twenty-three days after ceasing to take beer, no arsenic at all was detected in the viscera tested It is also stated that arsenic was detected in the urine fifty-nine days after any beer had been consumed The quantitative elimination of arsenic in the urine during consumption of solution of potassium arsenite is not known O'Leary, Snell and Bannick¹⁶ studied the excretion of a man who had arsenical cirrhosis and ascites as a consequence of the use of solution of potassium arsenite U S P About 10 mg of arsenic per liter of urine was found during the period of study In two cases of arsenic hepatitis (the type of arsenic used was not mentioned, but it was not neoarsphenamine), Young¹⁷ reported an average daily urinary excretion of 5 mg over about two weeks In studying a victim of criminal

12 Dutcher, R A., and Steel, M The Elimination and Retention of Arsenic as Determined by the Koch-Norton Method, *J Am Chem Soc* **36** 770-773, 1914

13 Scolosuboff Localisation dans les tissus d'animaux empoisonnés, *Bull Soc chim de Paris* **23** 124, 1875

14 McNally, W D The Retention of Arsenic in the Organs, *J Am Chem Soc* **39** 826-828, 1917

15 Garnier, L Experiences sur la recherche toxicologique de l'arsenic, These de Nancy, no 107, 1880

16 O'Leary, P., Snell, A M., and Bannick, E G Portal Cirrhosis Associated with Chronic Inorganic Arsenical Poisoning, *J A M A* **90** 1856-1859 (June 9) 1928

17 Young, A G Studies of the Action of Sodium Thiosulphate in Metallic Intoxications, *J Lab & Clin Med* **13** 622-628, 1927

poisoning, probably with arsenoxide, Fonzes-Diaçon and his associates¹⁸ recovered 242 mg of arsenic from the urine excreted in seven days

The common complications that occur during the therapeutic administration of solution of arsenoxide are three polyneuritis, keratosis and cirrhosis. These are usually preceded by so-called subtoxic phenomena and are generally accompanied with arsenical pigmentation of the skin. The polyneuritis appears to occur when the drug is given rapidly, and if ordinary care is taken in the instruction of the patient, it should not occur. The neuritic manifestations vary considerably. Paresthesias, radicular pain and ataxia come early. Later, if use of the drug is continued there is extreme weakness, which may progress to complete flaccid paralysis. In cases of acute involvement the neuritis has been so prominent that such diagnoses as Landry's paralysis and polyomyelitis have been made. Withdrawal of the drug is generally followed by complete but slow recovery of function. In Fonzes-Diaçon's patient profound weakness persisted for many months. Herpes zoster is common in patients chronically poisoned with inorganic arsenicals, and it may be the earliest sign of intoxication of the nervous system. The affinity of the drug for the central nervous system has been mentioned previously.

Cirrhosis with attendant ascites and occasionally jaundice is much more insidious. The first example of this complication given in medical writing was probably that of Bang's¹⁹ patient, who had hydrops and ascites and who recovered under a diuretic regimen. In 1895 Hutchinson²⁰ reported on a patient who had taken potassium arsenite for psoriasis for eight years. There were palmar and plantar keratoses and ascites, with a large tender liver. The patient recovered from the ascites when the arsenic was withdrawn. Hutchinson was apparently the first physician to state that cirrhosis and ascites can be due to arsenic. Geyer,²¹ who reported at great length on the cutaneous lesions of the victims of the epidemic of arsenic poisoning due to contaminated water in Reichenstein, in Schlesien, Germany, described several instances of ascites in patients with enlargement and tenderness of the liver. He also mentioned the cutaneous and the fatty hepatic changes in the

18 Fonzes-Diaçon, Grynfeldt, E., Rimbaud, L., and Cavalié. Sur un triple empoisonnement par l'arsenic, *Ann de méd lég* **15** 28-52, 1935

19 Bang, F. L. De hydropse ex ingesto arsenico observatio, *Soc med Havn collect* **1** 307-309, 1774

20 Hutchinson, J. Diet and Therapeutics, *Arch Surg*, London **6** 389-391, 1895

21 Geyer, L. Ueber die chronischen Hautveränderungen beim Arsenicismus und Betrachtungen über die Massenerkrankungen in Reichenstein in Schlesien, *Arch f Dermat u Syph* **43** 221-280, 1898

patients at autopsy. He described the cirrhosis and in the critical bibliography accompanying the article gave a reference to an experimental study of arsenic intoxication in animals by Ziegler and Obolonsky.²² They observed portal fibrosis but concluded that it was not typical portal cirrhosis. In the Manchester epidemic of 1900 many of the victims when first examined showed tenderness and enlargement of the liver, with ascites. Since that time there have been many reports of arsenical hepatitis from the ingestion of small amounts of inorganic arsenicals, either therapeutically or accidentally.²³ Arsenic was so generally recognized as a cause of chronic hepatic damage that Rolleston²⁴ listed it as one of the etiologic agents of portal cirrhosis. The most recent contribution was that of O'Leary, Snell and Bannick,¹⁶ who reported on two patients who had taken solution of potassium arsenite intermittently for several years and who recovered successfully from the ascites that developed.

The first description in the medical literature of the appearance of cutaneous lesions concurrent with the therapeutic use of arsenic was given in 1847 by Thomas Hunt,²⁵ who described the characteristic arsenic dermatitis. Since that time a variety of cutaneous lesions have been shown to be the result of the ingestion of inorganic arsenicals, and the deposition of arsenic in the skin has been recognized. Commonest are diffuse erythema and macular lesions. Less frequent are melanoderma and pustular lesions. A late result of exposure is the diffuse brownish red pigmentation, seen commonly among employees of chemical plants and others chronically poisoned. Herpes zoster is more properly considered a neurologic complication. In 1868 Erasmus Wilson²⁶ published a paper describing a certain type of keratosis which was painful at first and which occurred only among patients taking arsenic. J. C. White,²⁷ in 1885, reported the sequence of psoriasis, keratosis and malignant epithelioma in a physician who had taken solution of potassium arsenite for twenty-two years. White did not attribute

22 Ziegler, E, and Obolonsky, N. Experimentelle Untersuchungen über die Wirkung des Arsens und des Phosphors auf die Leber und die Nieren, *Beitr. z. path. Anat. u. Physiol.* **2** 291-336, 1888.

23 Broadbent, W. Hodgkin's Disease and Arsenical Poisoning, *Brit. M. J.* **1** 1140-1141, 1903. Hamburger, L. P. Arsenical Pigmentation and Keratosis, *Bull. Johns Hopkins Hosp.* **11** 87-91, 1900. Stockman.⁹

24 Rolleston, H., and McNee, J. W. Diseases of the Liver, Gall-Bladder and Bile-Ducts, ed. 3, New York, The Macmillan Company, 1929, p. 215.

25 Hunt, Thomas. Further Observations on the Administration of Arsenic, *Lancet* **1** 92, 1847.

26 Wilson, E. Clinical Memoranda, *J. Cutan. Med.* **1** 354, 1867-1868.

27 White, J. C. Psoriasis, Verruca, Epithelioma. A Sequence, *Am. J. M. Sc.* **89** 163-173, 1885.

the malignant lesion to the therapy, but Jonathan Hutchinson,²⁸ who saw the patient later, did and subsequently reported on six patients with cancer of the skin who had taken solution of potassium arsenite for from eight to twenty-two years. There was no question in his mind of the validity of the relationship, and he unhesitatingly advised the discontinuance of the drug when keratosis occurred.

The cutaneous, neural and visceral lesions that result from overdoses of arsenoxide are different from the complications encountered when the more complex organic arsenicals are used. Arsphenamines and derivatives of arsanilic acid may cause exfoliative dermatitis but apparently not keratosis. Acute toxic hepatitis and acute yellow atrophy occur, but patients seldom survive long enough or are dosed thoroughly enough to show hepatic fibrosis, except as a reparative phenomenon. Widespread damage to the capillaries, with purpura, is seen, and a rare and often fatal syndrome—*aleukia haemorrhagica* (Franck)—occurs. There is no counterpart for this among the complications of arsenoxide therapy. However, the routine use of these organic drugs is not associated with leukopenia, and it is generally recognized that organic arsenicals do not benefit leukemic patients. The amount of metallic arsenic which a patient receives daily is about the same with the two types of drug, and Young¹⁷ found that the daily urine of these patients contained about 5 mg of arsenic shortly after cessation of therapy, a value that compares well with the excretion of arsenic reported by O'Leary and his associates. The reasons for the difference in the activity of the various forms of arsenic have not been elucidated, although Voegtlin²⁹ noted that arsenoxides depressed the *in vitro* consumption of oxygen of normal tissues more than did equivalent amounts of arsanilic acid and arsphenamine derivatives.

The effect of arsenoxide on the leukocytes has been known since Cutler and Bradford,³⁰ in 1878, using the newest methods for making blood counts, gave solution of potassium arsenite to normal persons, anemic patients and to one man with chronic myeloid leukemia. In the patient with myeloid leukemia a striking remission occurred, the leukocyte count dropped from 1,073,000 to 8,700 in ten and a half weeks. The drug was then discontinued for seven weeks, and the leukocyte count increased to 621,000. Five weeks more of arsenic administration returned the count to 84,000. The normal persons showed a slight

28 Hutchinson, J. On Some Examples of Arsenic-Keratosis of the Skin and Arsenic-Cancer, *Tr. Path. Soc. London* **39** 352-363, 1887-1888.

29 Voegtlin, C., Rosenthal, S. M., and Johnson, J. M. Influence of Arsenicals and Crystalline Glutathione on the Oxygen Consumption of Tissues, *Pub. Health Rep.* **46** 339-354 (Feb. 13) 1931.

30 Cutler, E. G., and Bradford, E. H. Action of Iron, Cod-Liver Oil and Arsenic on the Globular Richness of the Blood, *Am. J. M. Sc.* **75** 74-84, 1878.

decline in the leukocyte count with comparable quantities of the drug. In 1880, however, Delpuch³¹ reported that the administration of arsenic had no effect on the leukocytes. In Osler's text (first edition, 1892) was recorded a remission induced by solution of potassium arsenite in a patient with myeloid leukemia whose leukocyte count decreased from 500,000 to 4,000. Schwaer,³² in 1908, described a slight diminution in the leukocyte counts of patients with dermatologic and syphilitic disorders who were under treatment with inorganic arsenic compounds. Halter's¹⁰ finding of leukopenia in half of his patients treated with daily injections intramuscularly of arsenoxide has been referred to previously. Most of the studies of the action of arsenic compounds on the blood which have appeared in the twentieth century have been concerned with the effect of these chemicals on the erythrocytes—a subject that is beyond the scope of this paper.

SUMMARY

A study of the case reports presented here demonstrates that complications resulting from the administration of solution of potassium arsenite to patients with myeloid leukemia are not rare when the course is reviewed critically.

In case 1 there was widespread keratosis of the skin, with definite hyperkeratosis of the soles after five years of arsenical therapy. At autopsy a large fleshy wart was observed, and other smaller ones had diminished in size as a result of treatment with salicylic ointment. The high arsenic content of the liver seems to incriminate the medication as the cause of the portal fibrosis observed.

In case 2 erythema developed that lasted for one day after three months of arsenic therapy. Five months later there was fairly good evidence of ascites (due to hepatitis?) which subsided spontaneously.

In case 3 herpes zoster developed after six months of treatment with solution of potassium arsenite. After taking the drug almost continuously for two years the patient had transient neuritis of the legs with paresthesia and ataxia.

In case 5 there was tenderness of the soles after one year of treatment, and a diagnosis of arsenical keratosis was made. This condition improved spontaneously, and subsequent developments are not known.

In case 6 herpes zoster developed after three months of intensive arsenic therapy.

Therefore, five of the six patients presented at one time or another in the course of treatment with solution of potassium arsenite seven

31 Delpuch. De l'action d'arsenic sur le sang, These de Paris, no 315, 1880.

32 Schwaer, G. Ueber die Einwirkung therapeutischer Arsendosen auf die Leukozyten beim Menschen, mit besonderer Berücksichtigung der Atoxyl-Wirkung, Arch f Dermat u Syph 90 77-96, 1908.

complications known to result from arsenic. All these patients after taking the drug for longer than five or six months complained of a troublesome chronic cough, and examination of the chest frequently disclosed moist râles. It is not clear whether this was due to the arsenic or the leukemia. The importance of possible complications of this form of therapy in relation to the probable benefits from solution of potassium arsenite in leukemic patients is hard to judge. Certain it is that the disease for which the patients are being treated will ultimately be fatal, but the therapy should not increase their discomfort. Broadbent²³ recognized that the ascites seen so frequently in his time in patients with blood dyscrasia and Hodgkin's disease was often due to solution of potassium arsenite which they were taking. He was often pleased to find this troublesome disorder disappear when the medication was withheld. Therapeutically induced neuritis is just as uncomfortable and inconvenient to the patient as plantar and palmar keratoses or ascites. Since many patients readily tolerate enough arsenic to produce these complications without suffering unduly from the minor, so-called sub-toxic symptoms of conjunctival and nasal congestion and gastrointestinal disorders, the therapeutic principle is obvious. A patient should not be permitted to dose himself to his idea of tolerance with solution of potassium arsenite over long periods without medical supervision. Frequent examination of the soles and palms, frequent palpation of the abdomen and caution in proceeding with the drug when herpes zoster or paresthesia occurs are as necessary as a routine leukocyte count. The possibility that ascites is due to the therapy should be remembered, and when it occurs a long rest period, with administration of diuretic drugs, is indicated. If keratosis appears, we do not believe that permanent interdiction of arsenic—as recommended by Hutchinson—is indicated. Rather, the drug should be discontinued until the soreness leaves and then begun again cautiously. If the leukocyte count does not stay at a low level during the rest periods but rises so rapidly that solution of potassium arsenite must be taken almost continuously, roentgen therapy should be given.

The histories of the patients presented here suggest two other points of therapeutic value. Arsenic therapy and roentgen therapy are not antagonistic, and a remission of leukocytosis may be induced with arsenic as soon as the postirradiation decline of the leukocyte count ceases. Also, years of arsenic medication do not render a patient resistant to roentgen therapy. It is encouraging to note that the patient with a high leukocyte count and the patient with severe cytologic findings (case 2) may respond well to a regimen of arsenic alone. The employment of the twenty-one day cycle of increasing doses of solution of potassium arsenite, followed by twenty-one days of rest, seems to be the most

satisfactory method of giving the drug. With control of the course by making frequent leukocyte counts, especially at the onset of treatment, necessary adjustments of the doses are readily made. Finally, in consideration of the prognosis under either form of therapy, it appears that in patients with typical chronic myeloid leukemia the outlook is best when the hemoglobin and erythrocyte counts can be kept at the highest level. Vigorous effort to attain an approach to normality in this respect is highly important.

CONCLUSIONS

The results of treating six patients suffering from chronic myeloid leukemia with solution of potassium arsenite for prolonged periods are presented, and the value of this drug, either as an adjuvant to roentgen therapy or as the sole therapeutic agent, is affirmed.

In five of these patients the following signs of chronic inorganic arsenical intoxication were noted: herpes zoster, keratosis, cirrhosis and polyneuritis.

The differences in the susceptibility of patients to arsenic with respect to the development of serious complications is considered.

Certain therapeutic principles for the management of chronic myeloid leukemia are drawn from a study of this material.

DERMATOLOGIC MANIFESTATIONS OF THE LYMPHOBLASTOMA-LEUKEMIA GROUP

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LOS ANGELES

The dermatologic manifestations of the diseases of the lymphoblastoma-leukemia group are often typical, despite the fact that it may be impossible to establish the diagnoses by other clinical and hematologic investigations. For this reason the cutaneous lesions occurring in these diseases are worthy of serious and extensive investigation. Involvement of the epidermis, corium or subcutaneous tissue may be the initial manifestation noted by the patient.

Although in numerous excellent articles this subject has already been discussed, most dermatologists have devoted the major portion of their studies to a consideration of the histopathology, etiology and interrelationships of these diseases. The clinical picture of most of these diseases has been carefully described, but there is a scarcity of reports of large series of cases investigated from the standpoint of the cutaneous manifestations. Most authors have tended to group mycosis fungoides, lymphosarcoma, lymphogranulomatosis (Hodgkin's disease) and lymphatic leukemia under the generic term lymphoblastoma. Others have included numerous other conditions, such as Spiegler-Fendt's sarcoid and reticulo-endotheliosis.

These processes are probably etiologically related and certainly offer similar clinical and microscopic characteristics. However, it is unfortunate that the tendency to consider all of them as variants of the same process is gaining favor. Much valuable work has been carried out to establish the identity of the diseases, and this should not be lightly discarded. While an individual patient may show what appear to be different diseases of the same group at different stages of his illness, this is unusual. Lymphosarcoma may temporarily resemble lymphogranulomatosis pathologically, or vice versa, but the histologic criteria on which these diagnoses are based are not inflexible. The fact that any of these conditions may terminate with a leukemoid blood picture is probably not of great significance. Marked lymphocytosis or leuko-

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cytosis with the presence of numerous immature cells may be noted in other conditions besides those of the lymphoblastoma series

Three types of cutaneous lesions may be observed in patients suffering from diseases comprising the lymphoblastoma-leukemia group. These are the specific lesions, the toxic manifestations ("lymphoblastomids" and "leukemids") and the accidentally associated conditions. These are differentiated by clinical rather than by histopathologic criteria. The petechiae or furuncles of a patient with leukemia may contain

TABLE 1—*Frequency and Types of Cutaneous Involvement*

Disease	No of Cases	Cases of Cutaneous Involvement	Cases of Specific Lesions	Cases of Ids	Cases of Associated Lesions
Lymphogranulomatosis	156	83 (53 2%)	12 (7 6%)	51 (32 7%)	4 (2 5%)
Lymphosarcoma	122	29 (23 7%)	17 (13 9%)	23 (18 8%)	3 (2 4%)
Myeloid leukemia	90	43 (47 7%)	5 (5 5%)	47 (52 2%)	2 (2 2%)
Lymphatic leukemia	60	28 (46 6%)	5 (8 3%)	27 (45 0%)	1 (1 6%)
Acute leukemia*	6	3 (50 0%)	0	3 (50 0%)	0
Lymphoblastoma*	5	4 (80 0%)	3 (60 0%)	0	1 (20 0%)
Monocytic leukemia†	4	3 (75 0%)	2 (50 0%)	1 (25 0%)	0
Plasma cell leukemia	1	1 (100 0%)	1 (100 0%)	0	0
Reticulo endotheliosis	1	0	0	0	0
Totals	445	194 (43 5%)	45 (10 0%)	154 (34 6%)	11 (2 4%)

* More exact classification was impossible with the information at hand

† Probably a stage of myeloid leukemia

TABLE 2—*Types and Frequency of Specific Cutaneous Lesions*

Disease	No of Cases	Cases of Nodules	Cases of Exfoliative Erythroderma	Cases of Ulcers	Cases of Sinus Formation	Cases of Plaques
Lymphogranulomatosis	12	2 (16 6%)	8 (66 6%)	2 (16 6%)	2 (16 6%)	0
Lymphosarcoma	17	15 (88 2%)	0	2 (11 7%)	0	0
Myeloid leukemia	5	4 (80 0%)	0	0	0	1 (20 0%)
Lymphatic leukemia	5	2 (40 0%)	1 (20 0%)	1 (20 0%)	0	1 (20 0%)
Acute leukemia	0	0	0	0	0	0
Lymphoblastoma	3	1 (33 3%)	2 (66 6%)	0	0	0
Monocytic leukemia	2	2 (100 0%)	0	0	0	0
Plasma cell leukemia	1	0	0	1 (100 0%)	0	0
Reticulo endotheliosis	0	0	0	0	0	0
Totals	45	26 (57 8%)	11 (24 4%)	6 (13 4%)	2 (4 4%)	2 (4 4%)

leukemic cells and may therefore be considered as specific lesions from the histologic standpoint. However, they are obviously nonspecific clinically and are discussed under the ids. The third group includes psoriasis, senile angiomas, mercury dermatitis and other lesions encountered during this study. These are of no diagnostic importance.

The material forming the basis of this study was taken for the most part from the records of patients in the Los Angeles County Hospital. Table 1 offers the salient facts regarding the incidence of lesions of the skin and mucous membrane among these patients. Mycosis fungoides and Spiegler-Fendt sarcoid were not included, as this inves-

tigation is concerned with the cutaneous manifestations of the diseases that are usually studied by the internist

LYMPHOBLASTOMA CUTIS AND LEUKAEMIA CUTIS

Specific lesions occurred in 10 per cent of the patients comprising this series. Table 2 offers the statistical findings for this group. Obviously, broad generalizations cannot be drawn from a study of 45 patients, but certain trends that are indicated are of interest.

Lymphogranulomatosis—The characteristic cutaneous lesion in Hodgkin's disease is the so-called exfoliative erythroderma. This occurred in 66.6 per cent of the patients presenting specific cutaneous lesions. It is characterized by generalized erythema, exfoliation and infiltration. As the disease progresses the skin becomes hyperpigmented and inelastic. As a rule intractable pruritus accompanies this process. In 2 patients the involved lymph nodes became suppurative, and draining sinuses formed. This corresponds to the scrofuloderma of tuberculosis. One elderly woman presented an ulcer which had developed over a necrotic lymph node, while another patient presented a stellate ulceration of the buccal mucous membrane that histologically proved to be Hodgkin's disease. According to Senear and Caro,¹ ulceration may be secondary to necrosis of a cutaneous or subcutaneous nodule, to necrosis of lymph nodes and the overlying skin or to necrosis of large cutaneous tumors. The ulcerative type of lymphogranulomatosis is most likely to be confused with epithelioma, but biopsy can establish a definite diagnosis. Nodules were noted in only 2 patients in this series.

Lymphosarcoma—Specific cutaneous lesions are most commonly noted in lymphosarcoma (13.9 per cent), while the rids are least often seen (18.8 per cent) in this division of the group. Metastatic nodules constitute the most frequent dermatologic finding. These were noted in 88.2 per cent of the patients in this series with specific lesions. The nodules may be superficial or subcutaneous. They are firm but lack the extreme hardness of metastatic carcinoma. The lesions are usually bright red, although they may have a blue tinge. If the lesion is located deeply, the overlying skin may not be discolored. Occasionally, metastatic nodules may be noted in close proximity to the primarily involved lymph node. In contradistinction to lymphogranulomatosis, exfoliative erythroderma did not occur once among the 122 patients with lymphosarcoma. This, plus the rarity of nodules in Hodgkin's disease, allows the dermatologist to make a clinical differentiation between the two conditions and forms a link in the chain of evidence

1 Senear, F. E., and Caro, M. R. Ulcerative Hodgkin's Disease of the Skin, *Arch. Dermat. & Syph.* **35**: 114 (Jan.) 1937.

pointing to the individual identity of these two conditions. Ulcers, forming as a result of necrosis of lymph nodes, were the only other specific lesions noted in these cases.

Leukemia—The cutaneous lesions of myelogenous leukemia are just as distinctive as those of the two first-named conditions. The most characteristic manifestation is the presence of numerous blue to red or skin-colored shotty nodules that are most common on the trunk and upper extremities, although they may be generalized. Meicer² stated that in monocytic leukemia the nodules may vary in size and color from day to day. These lesions were noted on 8 of 161 patients with various types of leukemia. Grouping the myeloid and monocytic leukemias together, nodules of this type occurred in 6 of the 7 patients presenting specific lesions. The seventh had a localized infiltrated plaque. The appearance of leukemic nodules in the skin is believed to be of grave prognostic import.³ Sydenstricker and Phinzy⁴ reported an example of monocytic leukemia in which there were purple macules. According to Hollander, Kastlin, Permar and Schmitt,⁵ Burckhardt's⁶ patient offered the only example of erythroderma occurring in myelosis mentioned in the literature.

In lymphatic leukemia the incidence was fairly well distributed between nodules, ulcers, plaques and exfoliative erythroderma. Loveman⁷ stated that the cutaneous manifestations of lymphatic leukemia are more common than those of myeloid leukemia. Studied on a percentage basis, these two groups were about equal (46.6 versus 47.7 per cent), although specific infiltrations were more common in the former (8.3 versus 5.5 per cent). The patient with plasma cell leukemia presented an ulceration with a surrounding infiltrated red areola on the finger. A biopsy established the diagnosis, which was confirmed by examination of the blood smear and bone marrow. One woman with monocytic leukemia had dermatitis venenata after the local application of 3.5 per cent tincture of iodine, and numerous specific nodules soon

2 Mercer, S. T. The Dermatoses of Monocytic Leukemia, *Arch Dermat & Syph* **31** 615 (May) 1935.

3 Weil, P. E., and Isch-Wall, P. A Case of Chronic Myeloid Leukemia with Terminal Development of Cutaneous Tumors, *Bull et mém Soc med d hop de Paris* **47** 84 (Jan 26) 1931.

4 Sydenstricker, V. P., and Phinzy, T. B. Acute Monocytic Leukemia, *Am J M Sc* **184** 770 (Dec) 1932.

5 Hollander, L., Kastlin, G. J., Permar, H. H., and Schmitt, C. L. Myeloid Leukemia with Cutaneous Manifestations, *Arch Dermat & Syph* **29** 821 (June) 1934.

6 Burckhardt, J. L. Zur Frage der akuten myeloiden Leukämie, *Frankfurt Ztschr f Path* **6** 167, 1910-1911.

7 Loveman, A. B. Monocytic Leukemia Cutis, *South M J* **29** 357 (April) 1936.

formed in the affected area, converting it into a plaque that histologically exhibited infiltration with leukemic cells

Unclassified Lymphoblastomas—While this group included only 5 patients, 3 showed specific cutaneous lesions. The evidence at hand indicates that in 2 the conditions were probably examples of lymphogranulomatosis, while in the third patient the lesions were suggestive of mycosis fungoides. There was only 1 patient in this series with proved reticulo-endotheliosis and he presented no dermatologic manifestations.

LYMPHOBLASTOMIDS AND LEUKEMIDS

The incidence of ids in this series is shown in table 3, 154 patients (34.6 per cent) of the entire group displayed some type of nonspecific

TABLE 3—Types and Frequency of So-Called Ids

Lesions	Cases of Lympho- granulo- matosis	Cases of Lympho- sarcoma	Cases of Myeloid Leukemia	Cases of Lymphatic Leukemia	Cases of Acute Leukemia	Cases of Monocytic Leukemia	Total No of Cases
Cases	156	122	90	60	6	4	
Hemorrhagic lesions	4 (2.5%)	4 (3.2%)	27 (30.0%)	15 (25.0%)	2 (33.3%)	1 (25.0%)	53 (11.9%)
Pigmentation	15 (9.6%)	2 (1.6%)	2 (2.2%)	1 (1.6%)	0	0	20 (4.5%)
Stomatitis	1 (0.6%)	3 (2.4%)	11 (12.2%)	1 (0.6%)	1 (16.6%)	0	20 (4.5%)
Pruritus	12 (7.6%)	4 (3.2%)	0	2 (3.3%)	0	0	18 (4.0%)
Maculopapules	12 (7.6%)	0	3 (3.3%)	1 (1.6%)	0	0	16 (3.6%)
Herpes zoster	4 (2.5%)	1 (0.8%)	1 (1.1%)	1 (1.6%)	0	0	7 (1.5%)
Bullae, vesicles	3 (1.8%)	1 (0.8%)	2 (2.2%)	0	0	0	6 (1.3%)
Herpes simplex	1 (0.6%)	3 (2.4%)	0	0	0	0	4 (0.9%)
Furunculosis	0	1 (0.8%)	2 (2.2%)	1 (1.6%)	0	0	4 (0.9%)
"Eczema"	2 (1.2%)	0	0	0	0	0	2 (0.4%)
Lichenoid papules	0	1 (0.8%)	0	1 (1.6%)	0	0	2 (0.4%)
"Toxic erythema"	0	2 (1.6%)	0	0	0	0	2 (0.4%)
Macules*	0	0	0	1 (1.6%)	0	0	1 (0.2%)
Urticaria	1 (0.6%)	0	0	0	0	0	1 (0.2%)
Vaginal ulcers*	0	1 (0.8%)	0	0	0	0	1 (0.2%)

* Not described further

related eruption. As the question as to which lesions should be included in this category is a matter of opinion, the inclusion of some of them is rightfully open to discussion.

Hemorrhagic Tendencies—Petechiae and ecchymoses are by far the most common cutaneous lesions seen in leukemia. This is probably due to a decrease in the number of platelets in the circulating blood.

Of the 161 patients with leukemia 27.9 per cent displayed hemorrhagic tendencies, despite the fact that bleeding from the mucous membrane was not included in this tabulation. These lesions were usually noted in acute leukemia or in the terminal stages of the chronic leukemias. In comparison with these figures, dermal or subdermal hemorrhages were seen in only from 2.5 to 3.5 per cent of the patients with Hodgkin's disease or lymphosarcoma. The terminal hematologic picture in these conditions is likely to be that of aplastic anemia. At times vesicles, bullae, macules and papules may be coexistent.

Pigmentation—Hyperpigmentation is a common finding in lymphogranulomatosis but is comparatively rare in other diseases of the lymphoblastoma-leukemia group. It may be localized or generalized and varies markedly in intensity in different cases. According to Cole,⁸ the mucous membranes are usually spared. The pigmentation may be the residual of a former eruption. Treatment in the form of arsenic or irradiation may cause or accentuate this type of lesion. The possibility that the pigmentation is secondary to the pressure of an enlarged lymph node on the sympathetic nervous system or to involvement of the adrenal cortex by lymphoblastomatous tissue also must be considered.

Stomatitis—Under this heading are included all grades of involvement of the mouth, ranging from simple stomatitis to noma. As in the case of hemorrhagic tendencies, lesions of the oral cavity are at least four times as frequent in leukemias as in the related entities under discussion. The appearance of stomatitis, angina or unusual lesions in the mouth is an indication for a careful hematologic investigation.

Pruritus—Itching without the presence of visible lesions should lead one to suspect the presence of a member of this group. The pruritus is apt to be severe and intractable. According to Goeckerman and Wilhelm,⁹ the itching is characteristically experienced under the skin, but this point did not prove to be of great value in this series. The presence of essential pruritus is more suggestive of Hodgkin's disease than of any of the other conditions considered, although it must be admitted that more common etiologic factors for this distressing symptom are to be found outside the lymphoblastoma-leukemia group. The cause of pruritus in these diseases has not been established. Shelmire¹⁰ said he believed it to be due to the absorption of toxic substances from the altered lymph nodes. Golay¹¹ and Milian and Blum¹² said they considered it as being secondary to disturbances of the nervous system.

"Toxic Rashes"—In this group are included the erythemas, maculopapular morbilliform eruptions, "eczemas" and other nonspecific entities. Here, too, lymphogranulomatosis leads the list. The mechanism producing these lesions is unknown, and their clinical characteristics run the gamut from macules to papules to wheals to vesicles to bullae to

8 Cole, H. N. The Cutaneous Manifestations of Hodgkin's Disease Lymphogranulomatosis, *J. A. M. A.* **69** 341 (Aug. 4) 1917.

9 Goeckerman, W. H., and Wilhelm, L. F. X. Lymphoblastoma, California & West Med **44** 517 (June) 1936.

10 Shelmire, B. Hodgkin's Disease of the Skin, *South M. J.* **18** 511 (July) 1925.

11 Golay, J. Sur le rôle du système sympathique dans la pathogénie d'un grand nombre de dermatoses, *Ann. de dermat. et syph.* **3** 407, 1922.

12 Milian, G., and Blum, P. Prurigo lymphadénique. Sa nature nerveuse, *Bull. Soc. franç. de dermat. et syph.* **27** 5, 1920.

furuncles The furuncles might be placed in a separate group, for they are probably secondary to the lowering of the resistance resulting from the systemic disease. Examples of this group of conditions were noted in 7.6 per cent of the 445 patients comprising this series.

Herpes—Zoster occurred in 1.5 per cent of the patients. It was most common in lymphogranulomatosis, appearing in 2.5 per cent of the patients. As zona occurs in 1 or 2 per cent of all cases of cutaneous disorders,¹³ this is possibly of less significance than is usually considered to be the case. Craver and Haagensen¹⁴ reported 7 instances (2.1 per cent) of herpes zoster among 329 patients with lymphoblastoma, although they noted 7 per cent among patients with lymphosarcoma and 4.5 per cent among those with Hodgkin's disease. Halle¹⁵ found 11 examples of zoster generalisatus among 16 patients with lymphatic leukemia. In the leukemias the lesions tend to be hemorrhagic. The associated lymphoblastoma probably serves as a contributing factor to this virus infection. Lockwood, Johnson and Narr¹⁶ reported a case in which herpes zoster was the initial manifestation of a lymphogranulomatous involvement of a vertebra. The appearance of zona should serve as an indication for a roentgenographic investigation of the nearest vertebrae. Herpes simplex was seen in only 0.9 per cent of the patients, a figure that does not serve as an argument for the relationship of herpes simplex and this group of diseases.

Other Conditions—Jaundice and subcutaneous edema are common manifestations. However, they are not included in this series, as they are seldom considered from the dermatologic standpoint.

COMMENT

The frequency of cutaneous lesions in diseases of this group has varied in different series. The usually accepted figure for Hodgkin's disease is that of Ziegler,¹⁷ who noted cutaneous manifestations in 25 per cent of his patients. He found further that in from 5 to 12 per cent of the patients cutaneous eruptions constituted the presenting sign or symptom. Both Cole⁸ and Miller¹⁸ reported that 40 per cent of their patients with lymphogranulomatosis presented cutaneous lesions.

13 Corson, E. F., and Knowles, F. C. Unusual Cases of Herpes Zoster, *Arch Dermat & Syph* **5** 619 (May) 1922.

14 Craver, L. F., and Haagensen, C. D. Note on Occurrence of Herpes Zoster in Hodgkin's Disease, Lymphosarcoma, and the Leukemias, *Am J Cancer* **16** 502 (May) 1932.

15 Halle, H. Zoster and Leukemia, *Arch f Dermat u Syph* **159**:238, 1930.

16 Lockwood, I. H., Johnson, E. T., and Narr, F. C. Hodgkin's Disease with Bone and Skeletal Involvement, *Radiology* **14** 445 (May) 1930.

17 Ziegler, K. Die Hodgkinsche Krankheit, Jena, Gustav Fischer, 1911.

18 Miller, H. E. Lymphogranulomatosis Cutis, *Arch Dermat & Syph* **17** 156 (Feb) 1928.

Miller found only 2 patients with specific infiltrations among 55 patients. Bairon¹⁹ noted dermal complications in only 16 per cent of his 24 patients with Hodgkin's disease. While the incidence of cutaneous lesions is higher in lymphogranulomatosis in our series (53.2 per cent), the average for the entire group (43.5 per cent) agrees with the statistics of Cole and Miller. Our greater number of specific lesions may be accounted for partly by remembering that we included exfoliative erythrodermas in this group.

The question of the specificity of lesions may also be discussed, and it is here that the histologic versus the clinical point of view must be stressed. Previously we indicated that the finding of a specific infiltrate on the microscopic slide does not establish a lesion as being clinically specific. The examples of the petechiae and the furuncles were mentioned. Conversely, the lack of specific cells in histopathologic studies does not disprove the specificity on clinical grounds. In reviewing the literature, it was noted that some authors have considered exfoliative erythroderma as a specific lesion while others have claimed that it is a toxic manifestation of the lymphoblastomatous or leukemic process. Some have stated that the eruption may be nonspecific, even though cells typical of leukemia may be demonstrated at biopsy. Montgomery, in a discussion of Barney's²⁰ paper, reported the finding of lymphoblastomatous cells in the grossly normal skin of patients with diseases belonging to this group. If so-called specific infiltrates can be found in normal skin, one must question the wisdom of classifying lesions as specific or nonspecific on histologic evidence alone.

Clinically a nondescript eczematous lesion may evolve into a manifestation indistinguishable from postarsenical exfoliative dermatitis and then into typical erythroderma. We have seen this occur and feel that the various lesions merely represent different phases of the same process. In our patient histologic examination revealed a mild inflammatory infiltrate in the upper portion of the corium, with the development of spongiosis early and of a lymphoblastomatous infiltrate later. Miller¹⁸ reported the occurrence of specific nodules in a patient with clinically typical pityriasis rubra of Hebra. We have seen a blood picture resembling that of lymphatic leukemia develop in a patient with a similar condition.

In reviewing the tables showing the incidence of the exfoliative dermatitis-malignant erythroderma complex in lymphogranulomatosis, one is impressed by its frequent occurrence as well as by its rarity in lymphosarcoma and myeloid leukemia. It is more frequent in lymphatic

19 Barron, M. Unique Features of Hodgkin's Disease, *Arch Path* **2** 659 (Nov) 1926.

20 Barney, R. E. Leukemic Myelosis Associated with Specific Nodules in the Skin, *Arch Dermat & Syph* **27** 725 (May) 1933.

leukemia than in the splenomyelogenous form. Our study leads to the belief that this complex is of differential diagnostic importance and should be considered as a specific manifestation of this group of diseases, despite the fact that similar eruptions may be seen in conditions unrelated to this group.

It is impossible for a study of this type definitely to establish the pathogenic identity of this group of diseases. Admittedly, the dermatologic aspects may vary and seemingly change from one condition to another even as do the pathologic and hematologic characteristics. We can only point out that the cutaneous manifestations are often of distinguishing value if present. As stated previously, we believe that these diseases are separate entities.

It is interesting to note that a high percentage of our patients exhibited an obvious focus of infection. However, the results of tampering with the focal infection were in most instances disastrous. This is particularly true in leukemia. In 11 patients in this series dental extraction either precipitated or aggravated the condition. Elimination of foci was ineffectual in every instance in which it was attempted.

Study of this series reiterates the frequency of cutaneous complications among patients afflicted with conditions belonging to the lymphoblastoma-leukemia group. The frequency of so-called specific lesions was found to be much higher than is generally considered to be the case. In these cases careful dermatologic examination coupled with judicious resort to histopathologic study may save the patient the inconvenience and expense of a detailed laboratory and clinical investigation as well as the need for biopsy of a lymph node.

SUMMARY AND CONCLUSIONS

The results of a study of 445 patients suffering from conditions belonging to the lymphoblastoma-leukemia series is presented.

The specific cutaneous lesions are described and their differentiating characteristics noted. Briefly, Hodgkin's disease shows the exfoliative erythroderma complex, the metastatic nodules of lymphosarcoma and the shotty nodules of the face and upper extremity of myeloid leukemia.

The common ids are also discussed, and an attempt is made to explain their pathogenesis.

The importance of herpes zoster as an id is questioned.

An attempt is made to establish the specificity of the exfoliative dermatitis-malignant erythroderma complex.

The importance of dermatologic study in this group of diseases is stressed.

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METABOLISM OF SODIUM *d*-LACTATE

I UTILIZATION OF INTRAVENOUSLY INJECTED SODIUM *d*-LACTATE BY NORMAL PERSONS

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The object of these experiments was to study the utilization of sodium *d*-lactate by human beings both under normal conditions and in the presence of certain pathologic processes. *D*-lactic acid represents an intermediary stage in carbohydrate metabolism in the cycle involving striated muscle and liver. The confusion which has arisen concerning the conversion of lactic acid into glycogen is in part due to the failure to realize the difference in the nature of the utilization of the *d* and *l* forms. Thus, Meyerhof and Lohmann¹ pointed out that isolated hepatic tissue of the rat was able to synthesize carbohydrate from *d*-lactic acid but hardly from *l*-lactic acid. Cori and Cori² have pointed out that if 95 mg per hundred grams of body weight of *d*-lactic acid per hour is injected into rats, there occurs no appreciable increase in the lactic acid content of either the blood or the urine, while if the experiments are repeated with sodium *dl*-lactate, a considerable urinary excretion of lactic acid occurs. These authors found that from 40 to 95 per cent of the sodium *d*-lactate given orally or injected subcutaneously is retained as glycogen in the liver and none is excreted in the urine. In contrast to this they found that 30 per cent of the *l*-lactic acid is excreted in the urine and hardly any glycogen is formed in the liver. Himwich, Koskoff and Nahum,³ working with decerebrate dogs, found that the main site of formation of lactic acid was the muscle, while

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From the Medical Service of Dr George Baehr and the Division of Laboratories, Mount Sinai Hospital

1 Meyerhof, O, and Lohmann, K. Ueber den Unterschied von *d*- und *l*-Milchsäure für Atmung und Kohlehydratsynthese im Organismus, *Biochem Ztschr* **171** 421, 1926

2 Cori, C F, and Cori, G T. Glycogen Formation in the Liver from *d*- and *l*-Lactic Acid, *J Biol Chem* **81** 389, 1929

3 Himwich, H E, Koskoff, Y D, and Nahum, L H. Changes in Lactic Acid and Glucose in the Blood on Passage Through Organs, *Proc Soc Exper Biol & Med* **25** 347, 1928

the liver was chiefly concerned with its removal from the blood stream and probably with converting it into glycogen. This is highly probable, since Cori and Cori⁴ found that injections of epinephrine, which cause a disappearance of glycogen from the muscle in normal rats, lead to the formation of glycogen from lactic acid in the liver. Elias and Schubert⁵ and Janssen and Jost⁶ showed that the intravenous injection of sodium *d*-lactate and sodium *dl*-lactate into the intact dog produced no increase in muscle glycogen. They assumed, therefore, that the lactic acid thus introduced was converted into glycogen by the liver. Abramson, Eggleton and Eggleton,⁷ working with racemic sodium lactate, found that in the intact anesthetized dog neither the muscles nor the liver synthesizes glycogen or dextrose from this salt. They further found that from 7 to 40 per cent of the injected racemic salt is excreted unchanged in the urine, the concentration of urinary lactate depending on the rapidity of the administration and the amount of the sodium *dl*-lactate injected. In their experiments the carbon dioxide content of the blood was increased, the elevation persisting for several hours after the urinary excretion of lactate was completed. Hartmann and Senn⁸ studied the metabolism of sodium *dl*-lactate in children. They injected from 4 to 7 cc of a molar solution per kilogram of body weight intravenously. The sugar and carbon dioxide contents of the blood rose considerably, and about 18 per cent of the injected lactate was excreted as such in the urine, the remainder being completely utilized within two hours. Most of the injected lactic acid disappeared from the blood stream within one hour. Since the racemic salt is a mixture of both the *d* and the *l* form, they concluded that 80 per cent of the *d*-lactic acid is converted into glycogen while all the *l*-lactate is oxidized.

It seems from the brief summary presented that there is a distinct difference between the behavior of the *d* and that of the *l* form of lactic acid, most of the *d* form being converted into glycogen by the liver, while the *l* form is partially excreted in the urine and the remain-

4 Cori, C. F., and Cori, G. T. Mechanism of Epinephrine Action. Influence of Epinephrine on Carbohydrate Metabolism of Fasting Rats, with Note on New Formation of Carbohydrates, *J Biol Chem* **79** 309, 1928.

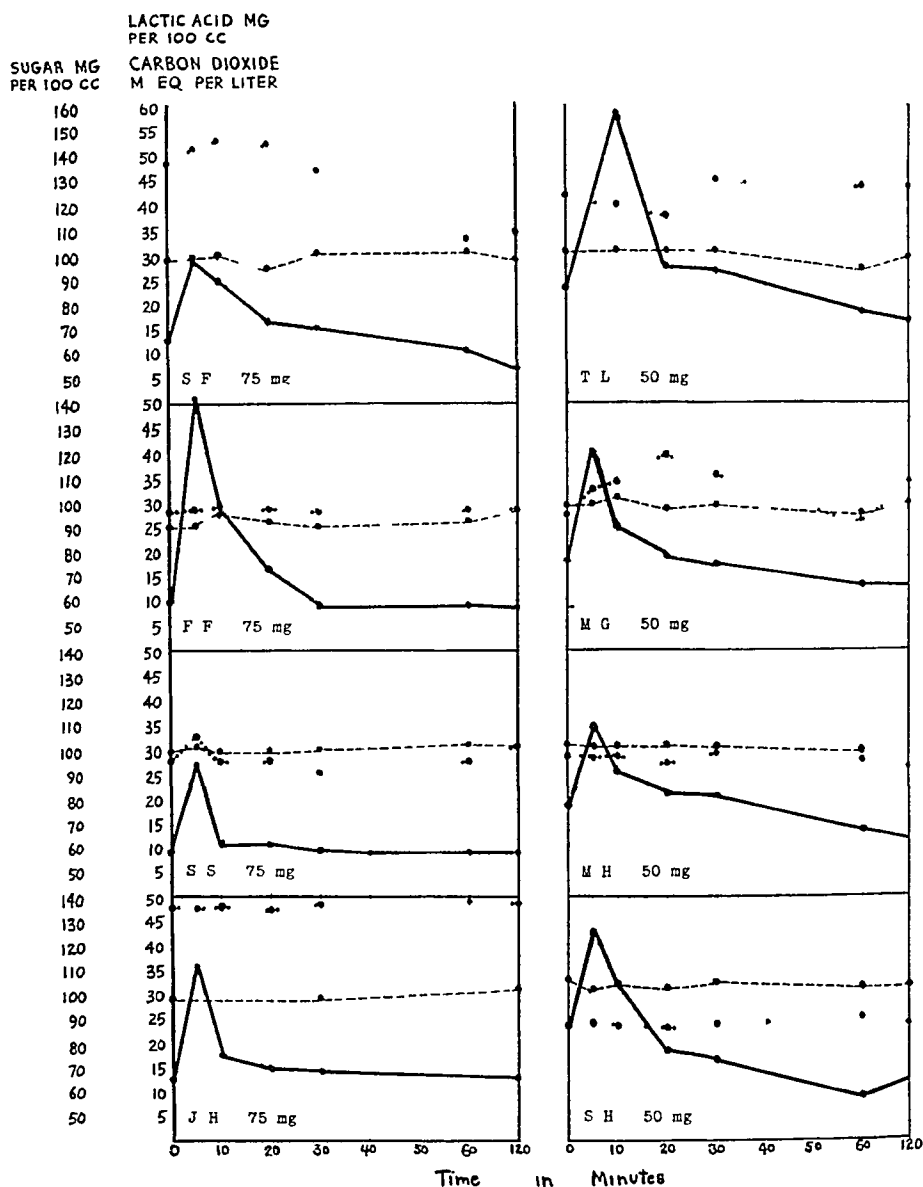
5 Elias, H., and Schubert, E. Ueber die Rolle der Saure im Kohlenhydratstoffwechsel. III. Saure und Muskelglykogen, *Biochem Ztschr* **90** 229, 1918.

6 Janssen, S. and Jost, H. Ueber den Wiederaufbau des Kohlenhydrates im Warmblutermuskel, *Ztschr f physiol Chem* **148** 41, 1925.

7 Abramson, H. A., Eggleton, M. Grace, and Eggleton, P. The Utilization of Intravenous Sodium *r*-Lactate. III. Glycogen Synthesis by the Liver, Blood Sugar, Oxygen Consumption, *J Biol Chem* **75** 745, 753 and 763, 1927.

8 Hartmann, A. F., and Senn, M. J. E. Studies in the Metabolism of Sodium-*r*-Lactate. I. Response of Normal Human Subjects to the Intravenous Injection of Sodium *r*-Lactate, *J Clin Investigation* **11** 327, 1932.

der is oxidized and apparently slightly, if at all, utilizable as a carbohydrate intermediary. As a corollary of this it follows that the proportion of the racemic salt which is converted into glycogen is essentially dependent on the amount of *d* salt present in the mixture.



Determinations on the blood. The solid line indicates the values for lactic acid, the dash line, those for carbon dioxide, and the dotted line, those for sugar.

METHOD

In the present series of experiments sodium *d*-lactate was used exclusively. The quantities injected were 50 and 75 mg per kilogram of body weight in a 14 per cent solution. This concentrated solution was employed in order to eliminate the prolonged time necessary for the injection of more dilute solutions. The persons on whom these studies were conducted were patients convalescing from

uncomplicated appendectomy or herniotomy. All the subjects selected were ostensibly normal except for the operative procedure. In each case at least from five to eight days was permitted to elapse after the operation before the experiments were started. The subject was kept in bed for twenty-four hours before the injection of sodium lactate and during the experiment. He was permitted no food for at least twelve hours before the experiment. A twenty-four hour specimen of urine was collected under toluene as a control, and the total quantity of urine voided during the two hour period of the experiment was used to determine the change in excretion of lactic acid following the injection of sodium *d*-lactate. All samples of blood were collected anaerobically under oil for the determination of the carbon dioxide content, while determinations of the lactic content were made on blood collected in sodium fluoride to prevent clotting and glycolysis. A control sample of blood was drawn, and with the needle in situ the solution of sodium *d*-lactate was then injected. The duration of the injection never exceeded two minutes. Samples of blood were collected five, ten, twenty, thirty, sixty and one hundred and twenty minutes after the injection. No undue reactions were observed in any of the patients.

All analyses were made in duplicate. Determinations of the lactic acid content of the blood and urine were made by the method of Friedemann and his colleagues⁹ and the carbon dioxide content of the blood by the method of Van Slyke and Neill¹⁰.

RESULTS

Lactic Acid in the Blood—After the injection of sodium *d*-lactate the increase in the lactic acid content of the blood above the control value varied from 15.6 to 41.2 mg per hundred cubic centimeters, the peak being reached at the end of five minutes. It seemed to make no material difference in the normal person whether 50 or 75 mg per kilogram of body weight of the test substance was used. After the peak the lactic acid content of the blood fell rapidly, the major drop occurring within twenty minutes, and more gradually thereafter, returning approximately to the control level within thirty minutes. In six of the eight subjects the lactic acid content fell below the control level. This occurred within from one-half to one hour after the injection.

Carbon Dioxide Content of the Serum—No appreciable change occurred in the carbon dioxide content in any of the experiments.

Blood Sugar—In only one instance did there occur a significant increase in the values for blood sugar after the injection. This occurred in patient M. G., who received 50 mg of sodium *d*-lactate per kilogram of body weight. In the remaining instances the values for blood sugar remained remarkably constant.

⁹ Friedemann, T. E., Cotonio, M., and Shaffer, P. A. Determination of Lactic Acid, *J. Biol. Chem.* **73** 335, 1927. Friedemann, T. E., and Kendall, A. I. Determination of Lactic Acid, *ibid.* **82**, 23, 1929.

¹⁰ Van Slyke, D. D., and Neill, J. M. Determination of Gases in Blood and Other Solutions by Vacuum Extraction and Manometric Measurement, *J. Biol. Chem.* **61** 523, 1924.

Results of Injections of Sodium d-Lactate

	Con trol	Minutes					
		5	10	20	30	60	120
J H , male aged 14, 75 mg per kilogram							
Blood lactic acid, mg per 100 cc	12 8	35 8	17 9	14 9	14 2		12 8
Blood sugar, mg per 100 cc	135 0	135 0	136 0	134 0	137 0	138 0	137 0
Carbon dioxide content, milliequivalents per liter	29 0				29 0		31 0
Lactic acid, mg per 100 cc							
Control 24 hr urine		16 8					
Urine voided during test (2 hr)		11 3					
S S , male aged 24, 75 mg per kilogram							
Blood lactic acid, mg per 100 cc	9 1	26 6	10 8	10 6	9 6	8 9	8 9
Blood sugar, mg per 100 cc	95 0	105 0	95 0	95 0	90 0	95 0	100 0
Carbon dioxide content, milliequivalents per liter	29 6	30 3	29 9	29 6	30 0	31 0	30 4
Lactic acid, mg per 100 cc							
Control 24 hr urine		31 7					
Urine voided during test (2 hr)		23 5					
F F , male aged 7, 75 mg per kilogram							
Blood lactic acid, mg per 100 cc	10 0	51 2	29 7	16 3	8 9	9 6	8 9
Blood sugar, mg per 100 cc	96 0	97 0	97 0	97 0	96 0	97 0	96 0
Carbon dioxide content, milliequivalents per liter	25 6	25 7	28 4	26 2	25 3	26 4	28 6
Lactic acid, mg per 100 cc							
Control 24 hr urine		14 0					
Urine voided during test (2 hr)		12 9					
S F , male aged 20, 75 mg per kilogram							
Blood lactic acid, mg per 100 cc	12 6	28 2	24 4	16 3	15 6	10 4	7 4
Blood sugar, mg per 100 cc	137 0	143 0	146 0	145 0	134 0	107 0	109 0
Carbon dioxide content, milliequivalents per liter	29 8	29 8	30 0	27 7	30 2	30 5	29 3
Lactic acid, mg per 100 cc							
Control 24 hr urine		9 3					
Urine voided during test (2 hr)		9 3					
T L , male aged 14, 50 mg per kilogram							
Blood lactic acid, mg per 100 cc	23 4		58 4	27 9	26 6	18 1	16 6
Blood sugar, mg per 100 cc	124 0		120 0	116 0	130 0	128 0	128 0
Carbon dioxide content, milliequivalents per liter	30 3		30 5	30 5	30 5	27 6	29 7
Lactic acid, mg per 100 cc							
Control 24 hr urine		7 4					
Urine voided during test (2 hr)		5 8					
M G , male aged 22, 50 mg per kilogram							
Blood lactic acid, mg per 100 cc	18 0	40 0	25 2	18 9	17 8	13 6	13 6
Blood sugar, mg per 100 cc	95 0	105 0	108 0	119 0	111 0	94 0	107 0
Carbon dioxide content, milliequivalents per liter	28 8	29 0	30 7	28 3	29 3	27 9	29 5
Lactic acid, mg per 100 cc							
Control 24 hr urine		11 9					
Urine voided during test (2 hr)		13 0					
M H , male aged 24, 50 mg per kilogram							
Blood lactic acid, mg per 100 cc	18 1	34 2	25 2	20 7	20 2	13 4	11 3
Blood sugar, mg per 100 cc	97 0	96 0	97 0	94 0	93 0	95 0	92 0
Carbon dioxide content, milliequivalents per liter	30 6	30 2	30 3	30 6	30 1	29 8	
Lactic acid, mg per 100 cc							
Control 24 hr urine		12 3					
Urine voided during test (2 hr)		18 6					
S H , male aged 42, 50 mg per kilogram							
Blood lactic acid, mg per 100 cc	23 9	42 3	32 0	18 4	16 6	9 1	11 6
Blood sugar, mg per 100 cc	87 0	89 0	87 0	86 0	88 0	90 0	88 0
Carbon dioxide content, milliequivalents per liter	32 8	31 2		31 4	32 3	31 7	31 7
Lactic acid, mg per 100 cc							
Control 24 hr urine		13 6					
Urine voided during test (2 hr)		12 3					

Lactic Acid in the Urine—In seven of the eight subjects there occurred no increase in the excretion of lactic acid in the urine after the injection of this substance intravenously. In one instance (M. H., who was given 50 mg per kilogram of body weight) the urinary excretion of lactic acid increased from 12.3 to 18.6 mg per hundred cubic centimeters.

CONCLUSIONS

Sodium *d*-lactate when injected intravenously into the normal subject disappears rapidly from the blood stream. That it is completely utilized is evidenced by the fact that there occurs no increase in the excretion of this substance in the urine, despite the fact that in most instances the renal threshold for lactic acid is exceeded.¹¹ On the basis of the available data cited, it seems to be definitely established that the disappearance of the injected sodium *d*-lactate is dependent on its removal from the blood stream by the liver and its conversion into glycogen. This is further substantiated by the data to be presented in a subsequent paper dealing with the utilization of this substance in the presence of hepatic damage.

SUMMARY

The intravenous injection of sodium *d*-lactate in doses of from 50 to 75 mg per kilogram of body weight is followed by a considerable rise in the concentration of lactic acid in the blood, which attains its peak at the end of five minutes and returns to the control level within one-half hour.

In six of the eight subjects the lactic acid content of the blood fell below the control level within from one-half to one hour after the injection.

In only one of the eight subjects did there occur an increase in the excretion of lactic acid in the urine after the administration of the sodium *d*-lactate.

No appreciable change in the carbon dioxide content of the serum occurred in any of the experiments.

In only one subject did there occur a significant rise in the blood sugar content after the injection of sodium *d*-lactate.

Mr. Roger Steinhardt rendered technical assistance in the experiments.

¹¹ Hewlett, A. W., Barnett, G. D., and Lewis, J. K. Effect of Breathing Oxygen-Enriched Air During Exercise upon Pulmonary Ventilation and upon Lactic Acid Content of Blood and Urine, *J. Clin. Investigation* **3**: 317, 1926.

METABOLISM OF SODIUM *d*-LACTATE

II UTILIZATION OF INTRAVENOUSLY INJECTED SODIUM *d*-LACTATE BY PATIENTS WITH ACUTE DIFFUSE PARENCHYMAL INJURY OF THE LIVER

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The metabolism of racemic sodium lactate in the presence of disease of the liver has been studied by Schumacher¹ and Hartmann and Senn². The two optically active enantiomer components constituting racemic lactate differ from each other, according to Cori and Cori,³ with regard to the manner of their biologic utilization. The *l* form when injected or ingested cannot be converted into glycogen or any intermediate carbohydrate, but its greater portion reappears in the urine, whereas the remainder may be accounted for by the formation of accessory carbon dioxide. On the other hand, *d*-lactate is converted into glycogen by the liver.⁴ Hartmann and Senn concluded that the degree of glycogen formation from racemic lactate depends on the proportion of the *d* form present in the mixture.

It seems, therefore, of importance to study the fate of the optically active components separately, especially that of the *d*-lactate, in normal and pathologic human metabolism. In a previous paper we^{4a} demon-

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1 Schumacher, H. Das Verhalten der Blutmilchsaure bei Leberkranken, *Klin Wchnschr* **37** 1733 (Sept 9) 1928.

2 Hartmann, A. F., and Senn, M. J. E. Studies in the Metabolism of Sodium *r*-Lactate. III. Response of Human Subjects with Liver Damage, Disturbed Water and Mineral Balance, and Renal Insufficiency to the Intravenous Injection of Sodium *r*-Lactate, *J Clin Investigation* **11** 345, 1932.

3 Cori, C. F., and Cori, G. T. The Mechanism of Epinephrine Action. I. The Influence of Epinephrine on the Carbohydrate Metabolism of Fasting Rats, with a Note on New Formation of Carbohydrate, *J Biol Chem* **79** 309, 1928.

4 (a) Soffer, L. J., Dantes, D. A., Newburger, R., and Sobotka, H. Metabolism of Sodium *d*-Lactate. I. Utilization of Intravenously Injected Sodium *d*-Lactate by Normal Persons, *Arch Int Med*, this issue, p. 876. (b) Cori and Cori.³

strated that sodium *d*-lactate injected intravenously into normal subjects in doses of 75 mg per kilogram of body weight disappears rapidly from the blood stream. The major drop in the lactic acid level of the blood occurs within twenty minutes, and within one-half hour it returns to its control level. In most instances the lactic acid content fell below the control value within one hour. The disappearance of the injected *d*-lactate is due essentially to its conversion into glycogen by the liver. There occurred no change in the carbon dioxide content of the serum, and in only one instance was there an increase in the urinary secretion of lactic acid.

In the present paper we are reporting the data obtained after the intravenous injection of sodium *d*-lactate into patients with diffuse hepatic disease. Only patients with clinically well defined acute diffuse damage to the hepatic parenchyma were employed. There has been no attempt at present to make a quantitative correlation between the clearance of lactic acid from the blood stream and the clinical severity of the hepatic disease.

PROCEDURE

Of the eight patients studied, three had catarrhal jaundice, four had arsphenamine icterus and one had cirrhosis of the liver with superimposed necrosis. Seventy-five milligrams per kilogram of body weight of sodium *d*-lactate in a 14 per cent solution was injected intravenously. The patients were all confined to bed for at least twenty-four hours before the injection and during the course of the experiment. No food was permitted for at least twelve hours before the performance of the test. A twenty-four hour specimen of urine was collected under toluene as a control, and the total urine voided during the two hour period of the experiment was used to determine the change in excretion of lactic acid following the injection of sodium *d*-lactate. All samples of blood were collected anaerobically under oil for the determination of the carbon dioxide content, while analyses of the lactic acid content were made on blood collected in sodium fluoride to prevent clotting and glycolysis. A control sample of blood was drawn, and while the needle was in situ the solution of sodium *d*-lactate was injected. Samples of blood were collected five, ten, twenty, thirty, sixty and one hundred and twenty minutes after the injection. No undue reactions were observed in any of the patients studied. All analyses were made in duplicate. Determinations of the lactic acid content of the blood and urine were made by the method of Friedemann and his associates,⁵ and the carbon dioxide content of the blood was determined by the method of Van Slyke and Neill.⁶

RESULTS

Lactic Acid Content of the Blood—After the injection of sodium *d*-lactate the increase in the lactic acid content of the blood above the

5 Friedemann, T. E., Cotonio, M., and Shaffer, P. A. The Determination of Lactic Acid, *J Biol Chem* **73** 335, 1927. Friedemann, T. E., and Kendall, A. I. The Determination of Lactic Acid, *ibid* **82** 23, 1929.

6 Van Slyke, D. D., and Neill, J. M. The Determination of Gases in Blood and Other Solutions by Vacuum Extraction and Manometric Measurement, *J Biol Chem* **61** 523, 1924.

control level varied from 13.6 to 39.4 mg per hundred cubic centimeters, the peak being reached at the end of five minutes. The disappearance of the injected lactate from the blood stream occurred slowly, thus, at the end of sixty minutes the lactic acid level was still

Results of Injections of Sodium d-Lactate

	Control	5 Min	10 Min	20 Min	30 Min	60 Min	120 Min
F D, Laennec's Cirrhosis with Acute Hepatitis							
Blood Lactic acid, mg per 100 cc	20.7	34.3	32.9		31.5	23.9	24.7
Sugar, mg per 100 cc	88.0	92.0	87.0		90.0	93.0	88.0
Carbon dioxide, m eq per liter	26.6	26.6	27.0		23.9	27.9	26.5
Urine Lactic acid, mg per 100 cc	33.7						30.1
J S, Catarrhal Icterus							
Blood Lactic acid, mg per 100 cc	20.5	38.6	35.9	30.9	29.9	28.2	23.6
Sugar, mg per 100 cc	136.0	131.0	134.0	135.0	134.0	131.0	137.0
Carbon dioxide, m eq per liter	25.8	25.8	26.2	27.5	27.3	25.8	27.3
Urine Lactic acid, mg per 100 cc	15.5						16.6
A P, Catarrhal Icterus							
Blood Lactic acid, mg per 100 cc	15.2	54.6	37.9	39.8	25.1	24.1	15.4
Sugar, mg per 100 cc	80.0	82.0	79.0	80.0	80.0	84.0	86.0
Carbon dioxide, m eq per liter	29.7	29.0	30.0	29.4	28.9	28.9	31.5
Urine Lactic acid, mg per 100 cc	17.7						17.8
M R, Arsphenamine Hepatitis							
Blood Lactic acid, mg per 100 cc	16.9	33.8	31.8	30.0	21.9	21.9	21.4
Sugar, mg per 100 cc	110.0	115.0	114.0	107.0	101.0	119.0	115.0
Carbon dioxide, m eq per liter	29.7	29.7	30.6	29.7	29.7	27.1	31.3
Urine Lactic acid, mg per 100 cc	13.2						25.5
J R, Arsphenamine Hepatitis							
Blood Lactic acid, mg per 100 cc	17.4	40.7	35.5	27.6	27.0	18.4	14.8
Sugar, mg per 100 cc	117.0	112.0		105.0	110.0	101.0	100.0
Carbon dioxide, m eq per liter	29.0			28.0	27.0	28.0	
Urine Lactic acid, mg per 100 cc	12.0						21.3
J Br, Arsphenamine Hepatitis							
Blood Lactic acid, mg per 100 cc	13.3	44.1	29.9	27.1	21.1	20.1	15.0
Sugar, mg per 100 cc	86.0	83.0	83.0	83.0	83.0	83.0	82.0
Carbon dioxide, m eq per liter	32.4	27.4	24.4		27.6	27.0	29.2
Urine Lactic acid, mg per 100 cc	22.9						34.2
J Ba, Arsphenamine Hepatitis							
Blood Lactic acid, mg per 100 cc	15.9	45.5	45.3		42.0	21.3	16.6
Sugar, mg per 100 cc	100.0	97.0	90.0		86.0	85.0	85.0
Carbon dioxide, m eq per liter	29.9	24.7	25.9		25.9	26.4	27.5
Urine Lactic acid, mg per 100 cc	18.7						20.6
E L, Catarrhal Icterus							
Blood Lactic acid, mg per 100 cc	11.8	30.3	23.1	25.8	24.0	23.4	20.6
Sugar, mg per 100 cc	94.0	95.0	93.0	92.0	93.0	104.0	103.0
Carbon dioxide, m eq per liter	26.1	25.2	25.4	25.5	26.0	22.8	22.4
Urine Lactic acid, mg per 100 cc	35.8						9.4

considerably elevated, and in five of the eight instances it had failed to return to its normal level at the end of two hours.

Carbon Dioxide Content of the Serum—There was no appreciable increase in the carbon dioxide content of the serum after the injection of lactate in any of the experiments.

Blood Sugar—There occurred no significant increase in the blood sugar level over the control level in any instance.

Lactic Acid in the Urine—In five of the eight instances no increase in the excretion of lactic acid in the urine occurred after the injection of the salt intravenously. In the remaining three cases the increase in the urinary excretion of lactic acid varied from 50 to 93 per cent.

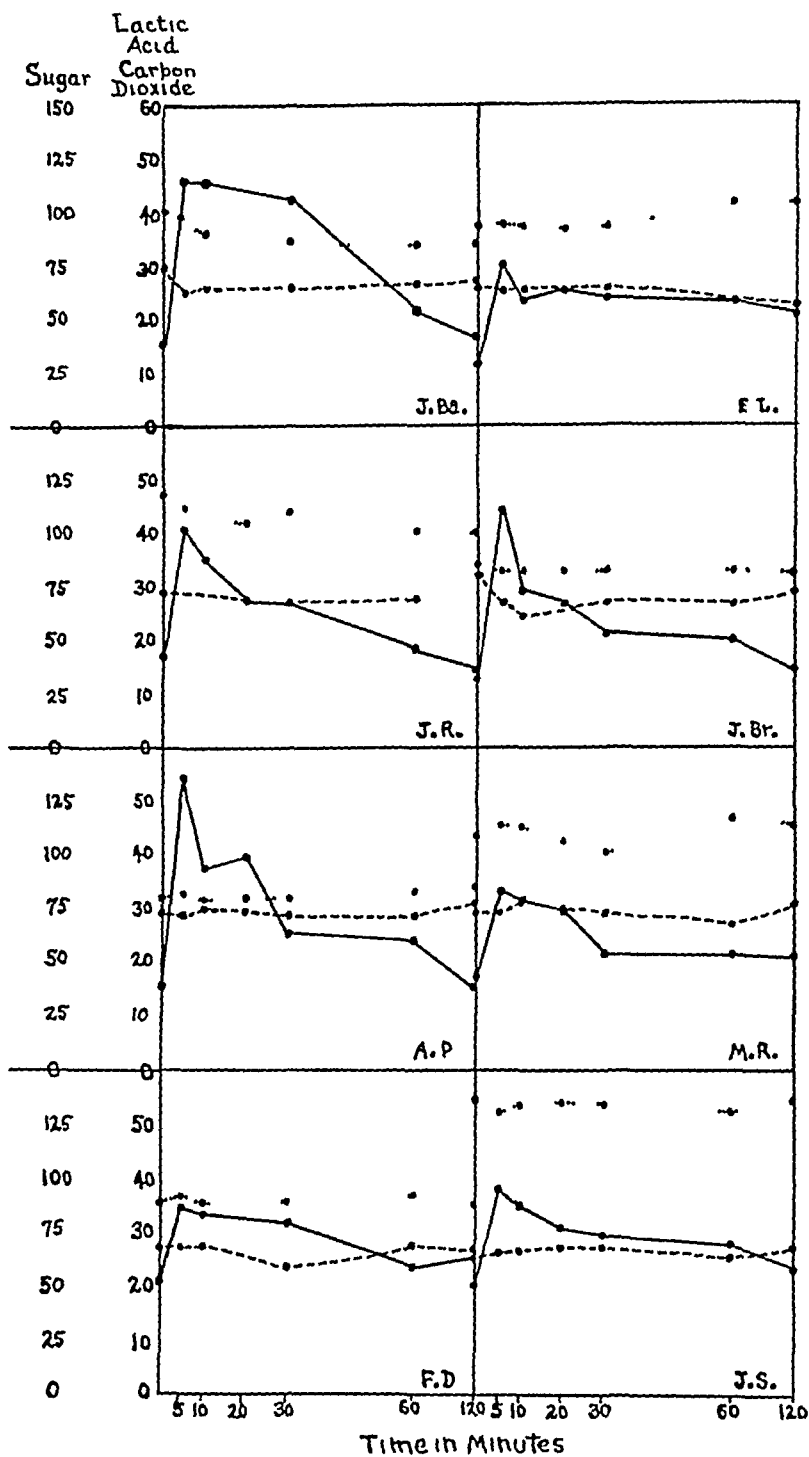


Chart showing the results of injections of sodium *d*-lactate. The solid line indicates the milligrams of lactic acid per hundred cubic centimeters of blood, the dash line, the carbon dioxide content of the blood in milliequivalents per liter, and the dotted line, the milligrams of sugar per hundred cubic centimeters of blood.

CONCLUSIONS

In normal persons the disappearance of intravenously injected sodium *d*-lactate occurred rather rapidly,^{4a} so that in all instances the lactic acid content of the blood returned to its approximate control level within one-half hour and fell below the control value within one hour. In the patients with hepatic damage presented in this series there occurred a definite delay in the disappearance of the injected lactate. Thus, at the end of thirty minutes the elevation of the lactic acid content of the blood above the control value varied from 30 to 164 per cent, while at the end of one hour it varied from 15 to 100 per cent. In only one case did the lactic acid content return to its control level within one hour. This occurred in patient J. R., who received only two thirds of the usual dose of sodium *d*-lactate.

In five of the eight instances the lactic acid content had still failed to return to its normal level at the end of two hours, the degree of retention varying from 13 to 74 per cent. In one patient there occurred a drop below the control level at the end of the two hour period. This occurred in the patient who received the reduced dose of sodium *d*-lactate.

One may conclude from these data that in the presence of acute diffuse hepatic parenchymal injury there occurs a definite delay in the utilization of intravenously injected sodium *d*-lactate. This delay is presumably due to the difficulty of conversion by the injured liver of the available *d*-lactate into glycogen.

SUMMARY

Sodium *d*-lactate in doses of 75 mg. per kilogram of body weight was injected intravenously in eight instances of acute diffuse hepatic parenchymal damage, and its rate of disappearance from the blood stream was investigated.

The lactic acid content of the blood remained elevated in all cases at the end of thirty minutes. The degree of retention of the injected lactate above the control value varied from 30 to 164 per cent, while at the end of one hour it varied from 15 to 100 per cent. In only one instance did the lactic acid level return to its approximate control value at the end of this period. This occurred in a patient who received only 50 mg. per kilogram of body weight. In five of the eight instances the lactic acid level was still considerably elevated after two hours.

In three of the eight patients there occurred an increase in the urinary excretion of lactic acid after the injection of the lactate.

No change occurred in either the carbon dioxide or the sugar content of the blood.

Progress in Internal Medicine

SYPHILIS

A REVIEW OF THE RECENT LITERATURE

PAUL PADGET, MD

AND

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BAITIMORE

This review covers publications which appeared during the last six months of 1936 and the first half of 1937. As before,¹ we have found it necessary to exercise a rigid selection of material and largely to exclude the literature on experimental syphilis and on serologic studies.

HISTORY OF SYPHILIS

As a part of the educational feature of the program for the control of venereal disease which is being developed, Winslow² and Moore³ present popular articles in which they briefly review the history of syphilis. Both emphasize that the means for the control of syphilis have been developed and need only to be applied. Moore and Manning⁴ studied the records of the Massachusetts Historical Society and discovered that many early settlements in New England were founded largely to secure sassafras for the London markets. It was in demand there as a remedy of many virtues, but chiefly for the treatment of syphilis. Zimmermann⁵ reproduces the first treatise on syphilis written

From the Syphilis Division of the Medical Clinic, the Johns Hopkins Hospital and University

1 (a) Moore, J. E. Syphilis. A Review of the Recent Literature, *Arch Int Med* **56** 1015 (Nov.) 1935. (b) Padget, Paul, and Moore, J. E. Syphilis. A Review of the Recent Literature, *ibid* **58** 901 (Nov.) 1936.

2 Winslow, C. E. A. The Drama of Syphilis, *J Social Hyg* **23**:57 (Feb.) 1937.

3 Moore, J. E. The Modern Background of Syphilis Control, *Hygeia* **15** 50 (Jan.) 1937.

4 Moore, Merrill, and Manning, Charles. Syphilis and Sassafras. Information Relating to the "Plant of the Sovereign Vertue for the French Pox" and Early Voyages to New England, *Am J Syph, Gonorr & Ven Dis* **20** 646 (Nov.) 1936.

5 Zimmermann, E. L. An Early English Manuscript on Syphilis. A Fragmentary Translation from the Second Edition of Gaspar Torrella's "Tractatus cum consiliis contra pudendagiam seu morbum gallicum," *Bull Inst Hist Med* **5** 461 (May) 1937.

in English and identifies it as a fragmentary translation from one of the consilia by Gaspar Torrella, of Toledo. Goodall⁶ points out that the fame of Fracastor should rest on more than his invention of the word syphilis. The treatise entitled "De contagionibus et contagiosis morbis et eorum curatione," says this author, entitles Fracastor to an important place in the history of epidemiology, because he there described theories both of the intimate nature of contagion and of the living nature of the cause of infection.

Wakefield, Dellinger and Camp,⁷ in a study of the skeletal remains of the mound builders of eastern Arkansas, discovered lesions of the long bones, clavicles, skulls and bones of the nose which were similar to the changes produced by syphilis. In one skeleton they found these changes in both tibiae, radius and ulnas, one fibula and the bones of the skull. They point out that this multiplicity of lesions is strongly in favor of syphilis as the cause, but they emphasize that the diagnosis of syphilis made solely by study of skeletal remains is always open to question, because there is no way to prove that the changes observed were not the result of some other chronic inflammatory process. Taking the long view, however, they conclude that whereas there is not enough evidence to say with certainty that precolonial Americans had syphilis, the probability is strong that they did. The authors are insistent, however, in avoiding the controversy regarding the New or the Old World origin of the disease.

SPIROCHAETA PALLIDA

Cultivation—Efforts to grow *Spirochaeta pallida* in pure culture continue, with an occasional enthusiastic preliminary communication, such as that of Schereschewsky.⁸ This author reports that he is able to maintain for many days the viability of *S. pallida* obtained from the spleens of infected white mice. There is presented, however, no evidence that multiplication occurs. Welferz⁹ is most enthusiastic, although her published results are even less convincing than those of Schereschewsky.

6 Goodall, E. W. Fracastor as an Epidemiologist, *Proc Roy Soc Med* **30** 341 (Feb) 1937.

7 Wakefield, E. G., Dellinger, Samuel C., and Camp, John D. A Study of the Osseous Remains of the Mound Builders of Eastern Arkansas, *Am J M Sc* **193** 488 (April) 1937.

8 Schereschewsky, J. Culture de spirochetes pâles provenant de la rate de la souris blanche, *Bull Soc franç de dermat et syph* **43** 1063 (June) 1936.

9 Welferz, Galina. Biologie du spirochete pâle, simple methode d'obtention du spirochete pâle dans une culture pure et les caracteres morphologiques des spirochetes dans les cultures, *Bull Soc franç de dermat et syph* **43** 1065 (June) 1936.

Morphology—Bessemans and his colleagues¹⁰ undertook to determine the reasons for the lack of agreement between the numbers of spirochetes to be found in material from a rabbit syphiloma by dark field study, on search of smears stained by the Fontana-Tribondeau method and on examination of sections stained by the Dieterlé method. In a large series of comparative studies they observed no characteristic differences between the results obtained by the three methods. They conclude, therefore, that the contradictions are apparent and not real.

In spite of this demonstration of the variability of the results obtained by any of the methods of rendering the spirochete visible, Bessemans¹¹ describes a method he has devised for counting spirochetes in a homogenized emulsion and experiments which are based thereon. These observations seem to indicate that chancres must contain many more demonstrable spirochetes than lymph nodes in order to be infectious. He postulates therefore that while *S. pallida* is morphologically a unit, it is functionally variable. This ingenious hypothesis is advanced not only as an explanation of certain anomalies to be observed in the course of the disease in animals experimentally infected with syphilis¹² but also as a counter in the long controversy with Levaditi,¹³ who explains similar phenomena by assuming the existence of an invisible form of the spirochete.

Tilden,¹⁴ by appropriate filtration experiments, demonstrated that *S. pallida* will pass through collodion membranes the pores of which have

10 Bessemans, A., Janssens, P., Van Thullen, E., and de Wilde, H. Affinités tinctoriales et argentiques du treponème pâle, *Bull. Soc. franç. de dermat. et syph.* **43** 1073 (June) 1936.

11 Bessemans, A. Sur la variabilité fonctionnelle de "*Treponema pallidum*," *Bull. Soc. franç. de dermat. et syph.* **43** 1084 (June) 1936.

12 Bessemans, A. La pathogénie de la syphilis inapparente chez le lapin, *Bull. Soc. franç. de dermat. et syph.* **43** 1111 (June) 1936. Bessemans, A., and de Moor, A. Ueber das Auftreten der *Spirochaeta pallida* (*Treponema pallidum*) im Gehirn und anderen Organen der mit asymptomatischer Lues infizierten Maus, *Dermat. Ztschr.* **75** 57 (March) 1937.

13 Levaditi, C., Vaisman, A., Schoen, R., and Manin, Y. Recherches expérimentales sur la syphilis (deuxième mémoire). Variations de l'activité pathogène et cycle évolutif du virus syphilitique, *Ann. Inst. Pasteur* **56** 251 (March) 1936. Levaditi, C., Vaisman, A., and Schoen, R. Recherches expérimentales sur la syphilis. Étude pathogénique de la neurosyphilis, *ibid.* **56** 481 (May) 1936. Levaditi, C., Vaisman, A., Schoen, R., and Manin, Y. Sort de "*treponema pallidum*" sous l'influence thérapeutique de l'arsenic et du bismuth, sa persistance dans les tissus des animaux réfractaires, *Bull. Soc. franç. de dermat. et syph.* **42** 1813 (Dec.) 1935. Levaditi, C., Schoen, R., and Vaisman, A. Étude expérimentale de la neurosyphilis. Influence des souches tréponémiques, *Compt. rend. Soc. de biol.* **122** 732, 1936.

14 Tilden, Evelyn B. Filtration of *Treponema pallidum* and *Treponema novyi* through collodion membranes, *J. Bact.* **33** 307 (March) 1937.

an average diameter of 0.4 micron. Turner¹⁵ reports the maintenance of viability of spirochetes in rabbit chancres frozen at -78°C for from four to six months. This is an important step forward in the study of experimental syphilis.

Dissemination—Raiziss and Severac¹⁶ point out that the rapidity with which *S. pallida* invades the blood stream after syphilitic infection has occurred is of considerable theoretical interest and of great practical importance in connection with the possibility of transmitting syphilis by blood transfusion. By means of a set of carefully conducted experiments they demonstrated that the organism enters the blood stream of the rabbit immediately after intratesticular inoculation. They conclude from these observations that the greatest care must be exercised to prevent the transmission of syphilis by the transfusion of blood from a donor who has been recently infected. It must be emphasized, however, that the forced distention of tissues and the consequent destruction of natural barriers to dissemination of the virus which occur during experimental inoculation are not analogous to the mode of infection in human beings. The results of these experiments are therefore not applicable to man.

The wide distribution of spirochetes in patients with early syphilis is shown by Frankl¹⁷. This author obtained serum for dark field examination from areas of apparently normal skin, either by cantharides blister or by sterile abrasion. Spirochetes were regularly present in the material from patients early in the course of syphilitic infection. Charpy¹⁸ presents an interesting report of a student who, fearing that he had been infected with syphilis, insisted on dark field examination of material from the area in which a minor abrasion had been sustained during coitus, two weeks before. The lesion had healed, but material expressed after scarification of the area contained many spirochetes. No organisms were seen in material expressed from other scarified areas of the genital mucosa.

15 Turner, T. B. The Preservation of Virulent *Treponema Pallidum* and *Treponema Pertenuis* in the Frozen State, *J. Clin. Investigation* **15** 470 (July) 1936.

16 Raiziss, George W., and Severac, Marie. Rapidity with Which *Spirochaeta Pallida* Invades the Blood Stream, *Arch. Dermat. & Syph.* **35** 1101 (June) 1937.

17 Frankl, J. Le treponeme dans la peau intacte des individus syphilitiques, *Rev. franç. de dermat. et de venerol.* **12** 196 (April) 1936.

18 Charpy, J. Constatations de "*Treponema pallidum*" sous la muqueuse génitale pendant la période d'incubation du chancre, *Bull. Soc. franç. de dermat. et syph.* **43** 32 (Jan.) 1936.

IMMUNITY IN SYPHILIS

The literature dealing with the multitudinous problems of immunity in syphilis is much too voluminous to be reviewed here in extenso. However, some experimental observations are important enough to require mention. By means of bilateral scrotal inoculation of syphilitic material into rabbits which at varying intervals previously had had a similar inoculation on one side, Gastinel and his co-workers¹⁹ produced further evidence for the development of local immunity early in the course of syphilitic infection. Tani and his collaborators²⁰ continued their efforts to demonstrate specific antibodies in the serum of men and of animals suffering from syphilis in various stages. From their most recent observations they feel convinced that antibodies always are present but are in much higher titer early in the course of the disease. Beck,²¹ however, was unable to demonstrate an increase in the spirocheticidal properties of human blood serum or cerebrospinal fluid after treatment with induced malaria, and in a later communication he²² presents results entirely contrary to those of Tani and his co-workers.

Jahnel²³ makes an interesting contribution, which would be more valuable if full protocols were provided. In attempts to infect a wide variety of animals with syphilis he fell on certain hibernating rodents, notably the *Siebenschlafei* (rellmouse), which derives its name from its custom of sleeping approximately seven months a year. This animal apparently will spontaneously recover from infection with syphilis during hibernation, but in warm weather the disease persists.

From the clinical standpoint current information and the necessary deductions therefrom are well summarized by Chesney.²⁴

Immunity or resistance to syphilis develops in man as a result of syphilitic infection. The development is gradual and never proceeds so far as that of most of the other immune reactions of human beings. The resistance is not absolute but is only partially effective, and the extent to which it develops varies in different patients. It does not appear to be a function of the humors of the

19 Gastinel, P., Pulvéris, R., and Collart, P. Recherches sur l'immunité régionale, *Bull Soc franç de dermat et syph* **43** 1141 (June) 1936.

20 Tani, R., and Ôgiuti, K. Das Wesen der Syphilisimmunität II. Die spirochatozide Fähigkeit des Syphilisserums, *Jap J Exper Med* **14** 457 (Oct 20) 1936. Tani, T., and Aikawa, S. Das Wesen der Syphilisimmunität III. Parabioseversuche mit Kaninchen, *ibid* **14** 465 (Oct 20) 1936.

21 Beck, A. Investigations on the Problem of Immunity Against *Spirochaeta Pallida* in General Paralytics Treated with Malaria, *J Ment Sc* **82** 254 (May) 1936.

22 Beck, A. The Occurrence of Protective Antibodies in Syphilis, *J Path & Bact* **44** 399 (March) 1937.

23 Jahnel, F. Les processus de guérison naturelle dans syphilis expérimentale, *Bull Soc franç de dermat et syph* **43** 1149 (June) 1936, Further Studies in Experimental Syphilis. The Efficacy of Natural Curative Factors, *Am J Syph, Gonorr & Ven Dis* **21** 18 (Jan) 1937.

24 Chesney, Alan M. Syphilis as a Problem in Immunity, *South M J* **29** 1230 (Dec) 1936.

body, and its development can be prevented by appropriate treatment. Once established, however, it is not immediately dissipated by antisyphilitic agents, if at all. While little is known of its mechanism, it is nevertheless a factor of great importance to the individual concerned. The very fact that the development of this resistance may be interfered with by active treatment in the early stages of the disease places a heavy responsibility upon the physician who undertakes to treat patients with early syphilis. He should clearly recognize that in instituting antisyphilitic therapy he is presuming to interfere with one of nature's own mechanisms, and he should realize that he is not justified in this interfering unless he can improve upon nature. He cannot improve upon nature unless he is prepared and willing to carry out energetic and persistent treatment in the attempt to eliminate the infection from his patient altogether. This is the one lesson which the study of immunity in syphilis makes clear. The conscientious physician will take heed of it.

SEROLOGY

Parran and others²⁵ present the second report of the Committee on Evaluation of Serodiagnostic Tests for Syphilis.

In it is described a project in which the directors of thirty state, municipal and private laboratories undertook fifty-one performances of nineteen separate serodiagnostic methods. Eight of these methods were those described by serologists who had participated in the first study to evaluate original tests. For each of these eight methods a control examination was performed by the serologist who originally described the test. The specimens submitted in the second project are not, of course, entirely comparable. Because of the difficulties encountered in collecting comparable samples for all participants, it was found necessary to establish four separate groups of serologists. The serologists in each group received comparable samples from the same series of donors. Since different donors were used in each series, comparison cannot be drawn between the percentages of sensitivity and specificity for the methods that were evaluated.

Careful study of the tables which are presented in the second report shows that in some of the state and local laboratories the performance of serologic tests does not compare favorably with the results achieved in the laboratories of the originators of the methods. In some of the former laboratories, false positive reports were made in from 3 to 9 per cent of specimens from nonsyphilitic persons. In others the sensitivity of the tests dropped to an alarmingly low percentage.

The results achieved in other state and local laboratories, however, are quite comparable to those obtained with the control performances.²⁶

The variation in the apparent reliability of different laboratories inspired even further comment.²⁷

Every clinician who uses the serologic tests for syphilis should assure himself that (a) the laboratory employed is under the direction of a competently trained

25 Parran, T, and others. Efficiency of State and Local Laboratories in the Performance of Serodiagnostic Tests for Syphilis, *Am J Clin Path* 7 20 (Jan) 1937, *Am J Pub Health* 27 15 (Jan) 1937, *Ven Dis Inform* 18 4 (Jan) 1937.

26 The Efficiency of Serodiagnostic Tests for Syphilis, editorial, *J A M A* 108 728 (Feb 27) 1937.

27 The Clinician and the Serologic Test for Syphilis, editorial, *J A M A* 109 134 (July 10) 1937.

serologist, that (b) intralaboratory check of the accuracy of the test in common use is constantly maintained by the performance of another test of approximately equal specificity and sensitivity, e g, a complement fixation test is checked by a flocculation test or vice versa, or a flocculation test checked by a different flocculation test, that (c) interlaboratory checks of the accuracy of the tests employed are periodically carried out by the exchange of specimens with a different laboratory, and that, (d) most important of all, the accuracy of the laboratory is constantly checked against the known clinical diagnoses of the patient from whom specimens are submitted. This implies a close association with a large syphilis clinic.

Hazen²⁸ acts as spokesman for the committee on evaluation of serologic tests of the cerebrospinal fluid for syphilis. Kline²⁹ reworks the material of the previous serologic conference and suggests a standard scheme for the interpretation of results of these conferences. Webb³⁰ reiterates the value of employing two or more tests in the serodiagnosis of syphilis. Taussig and Orgel³¹ and Ester³² provide further evidence that malaria may cause a false positive reaction to occur with an otherwise reliable serologic test for syphilis. Chargin and Rosenthal³³ note that the behavior of the serologic reaction sometimes gives little or no indication of the true course of events in patients with latent syphilis.

OTHER LABORATORY PROCEDURES

Blood—Vaiga³⁴ studied the blood picture in a total of 80 patients in various stages of syphilitic infection. Some of them had received treatment, but most had not. Nothing characteristic of the disease was discovered in the blood picture. The white corpuscles were normal or slightly decreased in number, and there was a tendency toward mild anemia of the hyperchromic type. Coruzzi³⁵ concludes that the sedi-

28 Hazen, H. H., Parran, T., Sanford, A. H., Sencar, F. E., Simpson, W. M., and Vonderlehr, R. A. The Evaluation of Serodiagnostic Tests for Syphilis upon the Spinal Fluid, *South M J* **30** 465 (May) 1937.

29 Kline, B. S. Evaluation of Results of Flocculation Tests for Syphilis in the Recent American Conference, *Am J Clin Path* **7** 139 (March) 1937.

30 Webb, E. L. The Practical Value of Employing More than One Laboratory Procedure in the Serodiagnosis of Syphilis, *J Lab & Clin Med* **22** 184 (Nov) 1936.

31 Taussig, E., and Orgel, M. N. The Kahn Test in Malaria, *J Lab & Clin Med* **22** 614 (March) 1937.

32 Ester, F. Sul comportamento di alcune sieroreazioni della sifilide sul siero di sangue dei non luetici inoculati sperimentalmente con malaria terzana benigna, *Gior di batteriol e immunol* **17** 502 (Oct) 1936.

33 Chargin, L., and Rosenthal, T. Paradoxical Behavior of Wassermann Test in Latent Syphilis, *J A M A* **107** 1374 (Oct 24) 1936.

34 Vaiga, A. Die Bewertung des Blutbildes bei Syphilis, *Arch f Dermat u Syph* **175** 214 (Feb 5) 1937.

35 Coruzzi, C. Sulla velocita di sedimentazione delle emazie nella lue e nel campo dermatovenerologico, *Gior di clin med* **16** 1540 (Dec 30) 1935.

mentation rate for patients with syphilis is so variable that the method is of no value in differential diagnosis

Cerebrospinal Fluid—Stary, Kral and Winternitz,³⁶ from a chemical study of the Pandy test, conclude that the test is not specific for globulin but that it precipitates all the proteins of the cerebrospinal fluid. They agree with others, however, on its clinical usefulness. Deadman, Elliott and Smith³⁷ advocate the use of colloidal carbon (Carter's black india ink no. 358) to replace other colloidal preparations in testing the cerebrospinal fluid. On the basis of the literature and his own experience in 1,301 cases Donati³⁸ concludes that the determination of the diastase content of the cerebrospinal fluid is of no practical value.

Robinson and Miller³⁹ discuss the differentiation between discoloration of the cerebrospinal fluid due to bleeding into the subarachnoid space and that due to compression of the spinal cord. In the former case, they say, the cerebrospinal fluid will give a positive reaction to the benzidine test, whereas in the latter instance it will give a negative reaction.

THE SOCIAL AND PUBLIC HEALTH ASPECTS OF SYPHILIS

Dissemination of Information—Anything approaching a complete summary of the publications directed toward education of the public on the basic facts concerning syphilis is beyond the scope of this review. One editorial comment,⁴⁰ however, summarizes the conservative view of the situation.

Publicity as to syphilis is now becoming widespread. Until recently, except for a brief three year period, nothing about the disease, not even its name, could be forced into the public press. Within the last two years, conservative and liberal newspapers and magazines alike had mentioned "syphilis" and had printed news stories, editorials or important feature articles concerning it. Now books are being published for the public and at least three leading magazines have scheduled articles for early appearance. In journalistic parlance, the subject is "hot."

Every one knows that a flood of misinformation may do more harm than good. Overemphasis on moral reform, on "social hygiene," and underemphasis on the more easily defensible medical approach are possibilities. Even more dangerous is the publication of such scientific misinformation as suggests (*Literary Digest*, Oct. 31, 1936) that syphilis may be "cured" by one inadequately studied method of treatment in three months, or by another in two weeks.

36 Stary, Z., Kral, A., and Winternitz, R. Zur Chemie den Liquorreaktion nach Pandy, *Ztschr f d ges Neurol u Psychiat* **157** 116 (Jan. 12) 1937.

37 Deadman, W. J., Elliott, F. J., and Smith, H. The Examination of Cerebrospinal Fluids by Colloidal Carbon, *Am J Clin Path* **7** 246 (May) 1937.

38 Donati, F. Il contenuto diastatico del liquor nelle malattie sifilitiche del neurasse, *Gior di clin med* **16** 1296 (Oct. 30) 1935.

39 Robinson, F. H., and Miller, B. N. On the Differentiation of Colored Cerebrospinal Fluids, *Am J M Sc* **191** 538 (April) 1936.

40 Education of the Public on Syphilis—A Warning! editorial, *J A M A* **108** 478 (Feb. 6) 1937.

Another serious danger is the fact that the publicity gives evidence of being concentrated within too short a period. Since current public interest is greater than can be satisfied by medical accomplishment, interest may evaporate faster than it can be appeased. Those who wish to educate will have shortly said all there is to say and will have nothing new to offer, only repetition. Editors and audience alike will treat the subject as the latest fad, wearying of it as quickly as they have wearied of such other great American fads as flagpole sitting or miniature golf. It is possible, and at the present rate likely, that the syphilis control program will be talked to death.

The dissemination of information to the members of the medical profession has been as energetically pursued and perhaps more judiciously managed. Vonderlehr⁴¹ summarizes the development of the program for the control of venereal disease, no small feature of which is provision for the training of those who wish to become proficient and the dissemination of information to members of the medical profession as a whole. Much of this has been by word of mouth, but Stokes⁴² has done yeoman service in making authoritative information available to all who care to read. Vonderlehr and Usilton⁴³ present the statistical point of view. They bring out that 100,000 adolescent children annually acquire syphilis before they are self-supporting and emphasize that the financial burden of the proper treatment of this group must not be left on the already overburdened shoulders of the practitioner, it must be shared by the local health officer, who also usually is in the best position to conduct the necessary contact investigation.

Moore⁴⁴ points out that the ultimate control of syphilis depends on the development of adequate facilities for treatment. Parran⁴⁵ properly remands the problem to the practitioner.

In the public health control of syphilis, the members of the [medical profession] have an opportunity each in his own community, to sponsor and support a great work for a high purpose, with assurance of good results to the public.

41 Vonderlehr, R. A. Recent Extension of Venereal Disease Control Work Through the Provisions of the Social Security Act, *Pub Health Rep* **52** 95 (Jan 22) 1937.

42 Stokes, J. H. (a) Education of Physician and Movement for Venereal Disease Control, *J A M A* **107** 866 (Sept 12) 1936, (b) The Control of Syphilis. Critical Examination of Some of Its Problems (Prosser White Oration), *Brit J Dermat* **48** 527 (Nov) 1936, (c) The Control of Syphilis, *Ven Dis Inform* **17** 315 (Nov) 1936, (d) Clinical Problems in Syphilis Control Today, *J A M A* **108** 780 (March 6) 1937.

43 Vonderlehr, R. A., and Usilton, L. The Mass Control of Syphilis, *South M J* **30** 281 (March) 1937.

44 Moore, J. E. Development of Adequate Treatment Facilities for Control of Syphilis, *J A M A* **107** 787 (Sept 5) 1936.

45 Parran, T., Jr. Public Health Control of Syphilis, *Ann Int Med* **10** 65 (July) 1936.

The Prevalence of Syphilis—There is no new information about either the incidence or the prevalence of syphilis based on a large scale study such as that of Usilton's⁴⁶ survey of the incidence and prevalence of syphilis and gonorrhea. Isolated reports of selected groups of the population indicate, however, that the accepted figures are of the correct order of magnitude. Bell⁴⁷ reports that somewhere between 3 and 25 per cent of the sick of Dallas, Texas, have syphilis. Roberts and Williams⁴⁸ conducted a survey to determine the prevalence of syphilis in Gibson County, Tenn. They rather wryly report that in spite of a program for the control of syphilis which has been in operation for ten years, the rate of prevalence of syphilis is 1.7 per cent for the white population and 10.8 per cent for the Negroes. Holloway, Grant and Bent⁴⁹ determined the incidence of positive results of serologic tests for syphilis in two groups of Negroes—clinic patients and a group of well students. Unfortunately, the arbitrary selection of material makes their study of little value for estimating the general incidence or prevalence of syphilis in the Negro population.

Scattered reports from abroad (excluding the Scandinavian countries) suggest that syphilis is as common there as here. Josa⁵⁰ found that 5 per cent of nearly 20,000 patients who were admitted to the surgical clinic of the Debrecen Hospital, Hungary, showed a positive reaction to a serologic test for syphilis. Hughes,⁵¹ however, discovered positive reactions to serologic tests for syphilis for only just over 1 per cent of Australian women who were pregnant.

The Functions of the Health Department in the Control of Syphilis—Reinhard⁵² offers a plea against a selective policy which serves to exclude patients with latent syphilis from treatment in health department clinics. He points out that this group presents an important and potentially serious problem if no facilities are provided by which the crippling

46 Usilton, L. J. Prevalence of Venereal Disease in the United States, *Ven Dis Inform* **11** 543 (Dec 20) 1930.

47 Bell, M. D. The Incidence of Syphilis in Dallas and Vicinity as Determined by Serological Methods. An Analysis of More than 39,000 Cases, *Texas State J Med* **32** 753 (March) 1937.

48 Roberts, F. L., and Williams, W. C. The Results of a County-Wide Survey and an Outline of the Syphilis Control Program in Gibson County, Tenn., *South M J* **30** 458 (May) 1937.

49 Holloway, G. D., Grant, W. H., and Bent, M. J. The Incidence of Syphilis in the Negro as Indicated by Serologic Tests, *Am J Syph, Gonorr & Ven Dis* **21** 303 (May) 1937.

50 Josa, L. Die Bedeutung der Syphilis in der Chirurgie auf Grund serologischer Untersuchungen, *Arch f klin Chir* **184** 299, 1935.

51 Hughes, T. D. The Result of the Routine Use of the Wassermann Test in 3,404 Patients Attending for Antenatal Care, *M J Australia* **2** 783 (Dec 5) 1936.

52 Reinhard, F. O. Late Latent Syphilis—A Problem and a Challenge, *J Social Hyg* **22** 360 (Nov) 1936.

late lesions of syphilis may be prevented from developing Vonderlehr⁵³ reemphasizes that the primary function of the Public Health Service and related agencies in the control of venereal disease is cooperation with the private practitioner

Programs for Syphilis Control Abroad—Freeman⁵⁴ recapitulates the Danish program for control of venereal disease, Vassaf⁵⁵ describes the campaign for the control of syphilis in Turkey, Yarros⁵⁶ is impressed by the accomplishments of the program in Moscow and Werr⁵⁷ proudly points to the healthier and happier families of Germany today

Syphilis and Life Insurance—In order to discover what life insurance companies are doing about syphilis Rein, Le Moine and Stephens sent a questionnaire to ninety-seven companies Their present report⁵⁸ is based on the seventy-five replies which they received Fifty-six (75 per cent) of those who replied stated that they occasionally requested a serologic test for syphilis "on suspicion," but only four companies had requested more than 100 tests in the preceding year Twenty-four companies had requested less than 10 or "very few" tests in the same period

Many of the respondents gave their reasons for not utilizing serologic tests for syphilis more frequently These reasons fall into three groups (1) the difficulty and expense which preinsurance serologic testing as a routine would involve, (2) the undesirable effect on the client which would be produced by demanding a serologic test and (3) the needlessness of making blood tests as a routine procedure

In examining the implications contained in their findings the authors bring out some startling facts Estimating that during 1935 about 2,500,000 persons applied for ordinary life insurance in the seventy-five companies and that probably 2 or 3 per cent of these had syphilis, the authors arrive at the conclusion that there were about 50,000 syphilitic applicants during the year which they are considering (1935) Only about 250 of these cases were detected¹

53 Vonderlehr, R A The Relationship of the Venereal Disease Control Work of the United States Public Health Service to the Physician in Private Practice, *Am J Syph, Gonorr & Ven Dis* **21** 32 (Jan) 1937

54 Freeman, C W Venereal Disease Control in Denmark, with Special Reference to Control of Syphilis, *J Social Hyg* **23** 189 (April) 1937

55 Vassaf, E The Syphilis Campaign in Turkey, *J Social Hyg* **23** 213 (April) 1937

56 Yarros, R S Moscow Revisited Social Hygiene 1930-1936, *J Social Hyg* **23** 200 (April) 1937

57 Werr, F Die Geschlechtskrankheiten im Ehegesundheitsgesetz, *Dermat Wchnschr* **104** 105 (Jan 23) 1937

58 Rein, C R, Le Moine, M, and Stephens, M G What Are Life Insurance Companies Doing About Syphilis? *J Social Hyg* **23** 258 (May) 1937

Syphilis in Industry—Gehrmann⁵⁹ reports the results of serologic tests for syphilis on 36,794 employees of a large corporation. Four per cent (1,488) were found to show a positive reaction. This author was particularly interested, however, in the course of events after a positive reaction to a serologic test for syphilis had been discovered. All positive reactions were verified. With few exceptions the result of the test was a matter of confidence between the employee and the laboratory. Each employee who manifested a positive reaction was referred to his physician or to a clinic for treatment. In following these patients to determine the adequacy of the treatment they had received, the author found the greatest variation in practice. Some physicians had refused to treat the patients, others were treating with pills alone while still others were extracting incommensurate fees from the luckless patients.

Syphilis and Unemployment—Syphilis in relation to employment has been the subject of editorial comment.⁶⁰

A potentially serious social situation is in process of creation by virtue of the current medical and lay interest in the campaign to control syphilis. The medical directors of certain large industrial corporations, and certain branches of the Federal Government itself, presumably stimulated by the recent wide publicity given to syphilis, are requiring routine blood tests of all applicants for positions, and are refusing employment to those found to have positive serologic tests for syphilis. In some instances, individuals already employed have been tested and, if found to be infected, dismissed.

The reason assigned for this procedure by certain corporation medical directors and lay officials who have been questioned regarding it are threefold: (1) the danger of transmission of syphilis to others (e. g., by food handlers), (2) the risk that a syphilitic person handling dangerous machinery may endanger the lives of others, and (3) the additional economic risk imposed upon the company by the possibility that the syphilitic individual may become disabled directly or indirectly because of his syphilis, thus imposing, through various forms of industrial compensation or other types of social insurance, the burden of his care upon the company (or Federal Government).

It is easy for the physician familiar with syphilis to show that, as related to the use of the routine blood test as a standard for employment, these arguments are fallacious.

(1) The danger of transmission of syphilis through nonsexual contact is slight indeed. Whatever small risk of infecting others may exist is for all practical purposes limited to the period before the diagnosis is made, and is over as soon as treatment is started.

(2) The risk that a syphilitic person handling dangerous machinery may endanger the lives of others is, for all practical purposes, limited to patients with cardiovascular or with neurosyphilis, and more particularly to those with

59 Gehrmann, G. H. Syphilis in a Large Industrial Organization, *Ven Dis Inform* 17:227 (Aug.) 1936.

60 Syphilis and Unemployment, editorial, *Am J Syph, Gonorr & Ven Dis* 21:339 (May) 1937.

paresis There is not the slightest evidence to indicate that industrial accidents are more frequently due to the carelessness of syphilitic persons (excluding the two classes named) than to that of nonsyphilitic workers The routine positive blood test does not establish the diagnosis of cardiovascular or neurosyphilis These diagnoses can be reached only after complete study of the patient

(3) The additional economic risk imposed upon the company by industrial compensation or other forms of social insurance is the greatest objection to the employment of syphilitic persons In this field the sweeping decision not to employ or to dismiss syphilitic individuals is based on inadequate information, or, if particular corporations do have adequate data covering the point, these data have not been made freely available in medical literature

So far as is known, there is (except in rare instances) no good evidence to indicate that a syphilitic worker who does not have cardiovascular or neuraxis involvement is any more likely (a) to be involved in accidents than his non-syphilitic brother, or (b) if involved in an accident, to suffer any more serious or prolonged disability, or (c) to suffer more severely from intercurrent non-syphilitic disease, or even (d) to undergo material shortening of his life span Whatever risk there may be of any of these eventualities may be largely guarded against (except in cardiovascular or neurosyphilis) by adequate treatment

The procedure by which an employer can best protect himself against possible loss from syphilis, and at the same time best serve society, is not therefore wholesale refusal to employ syphilitic workers, but individualization in each particular case

Finally, there are grave medical and social objections to class discrimination in the use of the routine blood test There is no adequate reason why this test should be limited to individuals employed in minor capacities The paretic executive is perhaps more likely to do harm to affairs of the company than the comptometer operator or the common laborer with latent syphilis If industry is to be consistent in this matter, it will begin the performance of routine serologic tests for syphilis with the president of the company, the board of directors, and the medical director, and will include all executives regardless of age, sex, salary, education, or social position If the laborer is to be fired solely because he has syphilis, so should the syphilitic executive be fired

The Epidemiology of Syphilis—The value of contact investigation in the control of syphilis has long been recognized It is unfortunate that application of this method of case finding in many places has been somewhat handicapped by lack of personnel and a feeling of futility Kulchar and Ninnis⁶¹ show, however, that every effort is worth while These authors attempted to trace the contacts of 244 patients with early syphilis By so doing they discovered 113 additional cases of fresh infection The Spillmanns⁶² emphasize the time factor in the epidemiology of syphilis On the appearance of the fifth man to give a history of infection by a blond prostitute, search for her was begun Before

61 Kulchar, G V, and Ninnis, E I Tracing the Source of Infection in Syphilis, *J Social Hyg* 22 370 (Nov) 1936

62 Spillmann, L, and Spillmann, A Résultats des enquêtes épidémiologiques effectuées dans le but de préciser l'origine des contaminations syphilitiques, *Bull Soc franç de dermat et syph* 43 1360 (July) 1936

she was found, however, at least 9 others had acquired syphilis from her Church ⁶³ graphically presents the tragedies which may result from failure to follow contacts

The investigation of contacts is not, however, always easy. The patient frequently is neither ready to disclose the name of his sexual partner nor willing to bring the partner to a physician or a clinic. Ingraham ⁶⁴ has been successful in overcoming this natural reticence by a technique which she describes as the persuasive approach.

Its aims with the syphilis patient are to gain his voluntary disclosure of identities of recent sexual intimates, to gain his voluntary services in personally recruiting them for medical examination, and to gain his voluntary agreement to our performance of this service. On the part of the "contact" the objective is that he voluntarily seek medical examination for syphilis. A trial of this noncompulsive method was rewarded with confidential disclosures from infected patients as to names and whereabouts of contacts and these were induced to be examined for syphilis as follows:

1. Of 201 patients with syphilis, 114 identified 174 exposures, an identification rate of 15 per cent contacts per productive case.

2. One hundred and thirty-seven ^{64a} (80 per cent) of the 174 persons sought were located, 128 (73.5 per cent) were recruited for examinations. Since 128 of the 139 ^{64a} contacts located were persuaded to report for study, persuasion was 92 per cent effective when the individual contact could be personally reached.

3. The type of community has little effect on the response of individuals, as evidenced by a comparison of these figures with those obtained by other writers elsewhere.

Brumfield ⁶⁵ provides a succinct summary of the salient features of the problem.

The Sources of Syphilitic Infection—Americans are so imbued with the Calvinistic theosophy that it is difficult for them to face and deal with facts which carry any taint of the immoral. It is perhaps for that reason that the only recent study of the source of syphilitic infection comes from Touraine and Chon ⁶⁶. In their experience in two large dispensaries in Paris these authors encountered 617 patients with recently acquired syphilis. In this group there were 385 men and 232

⁶³ Church, F. H. Transmission and Effects of Syphilis, *M. Rec.* **144** 323 (Oct. 7) 1936.

⁶⁴ Ingraham, L. B. The Persuasive Approach with the Infectious Syphilis Carrier. A Study in Public Health Method, *J. A. M. A.* **107** 1990 (Dec. 12) 1936.

^{64a} The discrepancy between these figures is not clear. From the original text apparently 139 contacts were located.

⁶⁵ Brumfield, W. A., Jr. The Epidemiologic Aspects of Syphilis Control, *South. M. J.* **30** 82 (Jan.) 1937.

⁶⁶ Touraine, M. A., and Chon. Les sources de contamination syphilitique (statistique personnelle d'après deux dispensaires), *Bull. Soc. franç. de dermat. et syph.* **44** 689 (April) 1937.

women Half the men had acquired the disease from street-walkers, most of the others had been infected during contacts thought to be safe The women, however, reported such variegated histories that few generalizations were possible

DRUGS

General Principles—Cole,⁶⁷ in a general discussion of the pharmacotherapy of syphilis, especially emphasizes four of the characteristics which a desirable antisyphilitic remedy should possess, once the necessary facts regarding its toxicity and therapeutic index are known

- 1 It should be cheap and readily available
- 2 It should be simple in form and in technic of administration
- 3 It should produce a minimum of untoward reactions, either immediate or delayed
- 4 It should be rapid in action

Throughout, this author takes the conservative stand regarding the adoption of new drugs or new principles in syphilotherapy and, for example, says concerning acetarsone "As yet I am unwilling to recommend the indiscriminate use of acetarsone in the treatment of congenital syphilis It is still too much in the experimental stage" To this statement Traisman⁶⁸ takes violent exception In reply Cole⁶⁹ carefully restates the proper attitude of conservatism to be adopted toward a new antisyphilitic remedy and gives the three reasons for his opinion of acetarsone

- 1 The antisyphilitic value of the drug is unproved
- 2 Published reports indicate that the drug is highly toxic
- 3 The use of acetarsone purports to do nothing which may not readily be accomplished by other means the worth of which is established

Rothermundt,⁷⁰ in an undocumented discussion of methods for the evaluation of antisyphilitic remedies, depreciates the value of biologic testing Only by clinical use, he says, may the value of an antisyphilitic drug be determined

⁶⁷ Cole, H N The Pharmacopeia and the Physician The Use of Antisyphilitic Remedies, J A M A **107** 2123 (Dec 26) 1936

⁶⁸ Traisman, A S The Use of Antisyphilitic Remedies, J A M A **108** 825 (March 6) 1937

⁶⁹ Cole, H N The Use of Antisyphilitic Remedies, J A M A **108** 825 (March 6) 1937

⁷⁰ Rothermundt, M Ueber die Bedeutung der biologischen Prüfung der Salvarsane, Deutsche med Wchnschr **62** 647 (April 17) 1936

Cannon⁷¹ and Harrison,⁷² on the basis of their wide personal experiences in syphilotherapy, speak for the superiority of arsphenamine over its derivatives in the treatment of patients with early syphilis. Harrison is reconciled to the abandonment of arsphenamine because of the difficulties attending its administration. Cannon, however, seeks ways to obviate or minimize these difficulties and so to retain the most potent drug in general use.

Moore and his collaborators⁷³ report the results of a comparison of the rate of reversal of the reactions to quantitatively titrated complement fixation tests for patients with early syphilis who were under treatment with various drugs. In a discussion of the general principles involved they say:

The evaluation of the worth of any antisyphilitic drug in man depends on a number of factors, some readily determinable within a few weeks of observation, others requiring shorter or longer periods ranging from a few months to a lifetime. The more important of these, assuming the factors of toxicity and general drug tolerance to be approximately equal, are:

- 1 The rate of disappearance of surface organisms from the moist lesions of early syphilis
- 2 The rate of healing of visible early and late lesions (or of symptomatic response in such conditions as neurosyphilis)
- 3 The rate of reversal of serologic reactions in early syphilis
- 4 The proportion of serologic resistance, i. e., Wassermann fastness, in early and late syphilis
- 5 The incidence of abnormal spinal fluids in treated patients with early syphilis
- 6 The incidence of serologic relapse in early syphilis
- 7 The incidence of early clinical relapse, especially infectious mucocutaneous relapse and neurorecurrence
- 8 The incidence of late progression or relapse
- 9 The permanence of clinical and serologic normality

The value of a given drug in the first of these respects may be determined within a few days, as to the second and third, within a few weeks, as to the fourth, fifth, sixth, and seventh, within a period ranging from a few months to three or four years, and as to the eighth and ninth, within many years to a lifetime. It is quite possible, furthermore, that a drug may be active in accomplishing disappearance of surface organisms, healing of lesions, and rapidity of early

71 Cannon, A. B. Optimal Treatment for Early Syphilis, Based on a Twenty Year Trial of Arsphenamine, Bismuth and Mercury Preparations, *Am J Syph, Gonorr & Ven Dis* **21** 155 (March) 1937.

72 Harrison, L. W. Experiences with Antisyphilitic Treatment from the Pre-Salvarsan Era to the Present and Their Possible Bearing on Present Treatment Practice, *Brit J Ven Dis* **13** 1 (Jan) 1937.

73 Moore, J. E., Hardy, S. M., Robinson, H. M., and Eagle, H. The Response of the Quantitatively Titrated Wassermann Test in Early Syphilis to Treatment with Five Different Arsenical Drugs, *Am J Syph, Gonorr & Ven Dis* **20** 503 (Sept) 1936.

serologic reversal, and yet be relatively unsatisfactory in respect to the other criteria named, and in particular to the most important of them all, the permanence of clinical and serologic normality

It will be noted that with few exceptions, the requirements enumerated apply almost exclusively to early syphilis. Excepting only the pentavalent arsenicals (tryparsamide, acetarson), it is true of all the other drugs used in syphilotherapy (i e, the trivalent arsphenamines, bismuth, and mercury) that their action in early syphilis is a reliable index of what may be expected of them in late syphilis. It is particularly true that so far as the rate of serologic reversal is concerned, early syphilis must be chosen as the prototype

They found that the average reduction in the titer of the complement fixation test in the blood of patients with early syphilis was approximately the same for treatment with four of the five drugs studied (arsphenamine, silver arsphenamine, bismarsen and mapharsen). The patients treated with neoarsphenamine, however, exhibited a somewhat slower reduction in reagin titer. These authors conclude, therefore, that since these five drugs are not of equal value with respect to other important results of treatment, the rate of serologic reversal for patients with early syphilis after treatment with a given drug can be regarded only as a relatively unimportant factor in the final evaluation of that drug.

Mapharsen —Since the publication of the original reports, previously referred to,¹ there has accumulated a considerable body of experience with the use of mapharsen in syphilotherapy. The largest series of patients treated with mapharsen is presented by Gruhzt, Dixon and their collaborators,⁷⁴ who report the results of the administration of 75,589 injections of the drug to 4,841 patients. These authors observed no severe reactions to the treatment in this series, and there were no deaths. Moderately severe reactions, which were almost entirely gastro-intestinal, occurred at the rate of 4.4 per thousand injections. To these authors the clinical and serologic outcome for the group as a whole was satisfactory, as compared with the expected course under other methods of treatment.

Kulchar and Barnett⁷⁵ present a detailed analysis of the results which they observed from the administration of 1,270 doses of mapharsen to 56 patients with early syphilis. They found that surface lesions of these patients healed more rapidly than those of patients treated with neoarsphenamine but that serologic reversal occurred more slowly than in the series of patients with early syphilis who had received arsphenamine who

74 Gruhzt, O. M., Dixon, R. S., and others. Mapharsen in Mass Treatment of Syphilis in a Clinic for Venereal Diseases, *Arch. Dermat. & Syph.* **34**: 432 (Sept.) 1936.

75 Kulchar, G. V., and Barnett, C. W. Mapharsen in the Treatment of Early Syphilis, *Am. J. Syph., Gonorr. & Ven. Dis.* **20**: 482 (Sept.) 1936.

were reported on by Moore and Kemp⁷⁶ Increased sensitivity of the serologic tests now employed, however, may well explain this apparent difference The incidence of neurosyphilis they found to be no less than that in groups of patients treated by other methods One unusual feature of the experience of these authors was the high incidence (14.7 per cent) of gastro-intestinal reactions

Astrachan⁷⁷ observed 158 patients treated with mapharsen Twenty-five of them had early syphilis, and the rate of healing of lesions was compared to that produced by neoarsphenamine From his results he concludes that mapharsen, while a useful antisyphilitic remedy, is less potent than neoarsphenamine Its use, he says, should therefore be limited to the treatment of patients with latent or late syphilis

Miller, Epstein and Simpson⁷⁸ discovered among 400 patients 31 who were intolerant to neoarsphenamine but who were given mapharsen without event and 2 for whom the reverse was true In addition, there were 6 patients who were intolerant to both drugs

Wieder and the Foersters⁷⁹ extend their earlier observations, which were reviewed previously,¹ and again conclude that mapharsen is a potent antisyphilitic remedy, with special properties which justify its continued use and study over an extended period Essentially similar conclusions are reached by Peterson,⁸⁰ Schmidt and Taylor⁸¹ and Parsons⁸²

Triarsen—Stokes and Beerman⁸³ report the observation of 189 patients who were given a total of 3,009 injections of triarsen From the results they conclude that this drug is suitable for use in the treatment of patients with early syphilis Certain of its properties, however, they feel should be studied further

76 Moore, J. E., and Kemp, J. E. The Treatment of Early Syphilis, *Bull Johns Hopkins Hosp* **39** 36 (July) 1926

77 Astrachan, G. D. Mapharsen in Antisyphilitic Therapy Preliminary Report, a Study Based on 3,386 Injections of Mapharsen, *Am J Syph, Gonorr & Ven Dis* **21** 81 (Jan) 1937

78 Miller, H. E., Epstein, N. N., and Simpson, R. G. Mapharsen Its Use in the Treatment of Syphilis, *California & West Med* **45** 321 (Oct) 1936

79 Wieder, L. M., Foerster, O. H., and Foerster, H. R. Mapharsen in the Treatment of Early Syphilis Further Experiments, *Arch Dermat & Syph* **35** 402 (March) 1937

80 Peterson, S. C. The Use of Mapharsen in the Treatment of Syphilis, *Canad M A J* **36** 172 (Feb) 1937

81 Schmidt, E. E., and Taylor, G. G. The Treatment of Syphilis with Mapharsen, *Am J Syph, Gonorr & Ven Dis* **21** 402 (July) 1937

82 Parsons, R. P. An Estimate of Arsenoxide (Mapharsen) in the Treatment of Early Syphilis, *U S Nav M Bull* **35** 207 (April) 1937

83 Stokes, J. H., and Beerman, H. New Arsphenamine Synthetics in Treatment of Syphilis A Consideration of Test Procedure and of a New Drug (Triarsen), *Arch Dermat & Syph* **35** 78 (Jan) 1937

Tryparsamide —Vonkennel and Kimmig⁸⁴ report attempts to demonstrate arsenic in the cerebrospinal fluid after the intravenous injection of therapeutic doses of tryparsamide. No arsenic could be recovered from the cerebrospinal fluid of any of 16 patients so treated. Further investigation showed also that this apparent impermeability of the blood-brain or blood-cerebrospinal fluid barrier was not altered after therapeutic malaria.

Bismuth —In his general discussion of syphilotherapy Cole⁶⁷ points out that there are many bismuth preparations available and advises the physician to learn the action of but a few of the well tried ones of known dependability. For use as a routine he advises a suspension of bismuth subsalicylate in oil, because of its slow, constant action. Under circumstances in which a more rapid action is desired, the use of one of the water-soluble preparations is recommended, but the author emphasizes that for therapeutic effectiveness these must be given thrice weekly.

Hanzlik⁸⁵ objects to the use of insoluble bismuth compounds on certain theoretical grounds but offers no facts to substantiate his opinion.

Johnson and Barnett⁸⁶ report the results of the examination of the cerebrospinal fluid of 120 patients with early syphilis who had received iodobismutol to the exclusion of other heavy metal preparations, in alternation with courses of neoarsphenamine or mapharsen. They discovered that 16 patients (13 per cent) had an abnormal cerebrospinal fluid. This coincided so closely with the incidence of neurosyphilis (13.8 per cent) in patients with early syphilis observed by Moore and Faupel⁸⁷ that the authors conclude

The substitution of iodobismutol for other heavy metal preparations in the routine treatment of patients with primary and secondary syphilis does not eliminate the problem of central nervous system involvement.

The rationale of prohibiting the use of alcoholic beverages by patients with syphilis, especially neurosyphilis, is called into question by the experimental observations of Newman and Richardson⁸⁸. These authors

84 Vonkennel and Kimmig. Arsenbestimmungen im Liquor nach Verabreichung funfwertiger Arsenpräparate, *Klin Wchnschr* **16** 603 (April 24) 1937.

85 Hanzlik, P. J. Insoluble Bismuth Compounds in Antisyphilitic Treatment, *J A M A* **106** 1985 (Dec 12) 1936.

86 Johnson, G. S., and Barnett, C. W. The Effect of Iodobismutol upon Spinal Fluid Findings in Early Syphilis, *Am J Syph, Gonorr & Ven Dis* **20** 651 (Nov.) 1936.

87 Moore, J. E., and Faupel, M. Asymptomatic Neurosyphilis. V. A Comparison of Early and Late Asymptomatic Neurosyphilis, *Arch Dermat & Syph* **18** 99 (July) 1928.

88 Newman, H. W., and Richardson, A. P. The Effect of Alcohol on Penetration of Bismuth into the Central Nervous System, *Am J Syph, Gonorr & Ven Dis* **21** 77 (Jan.) 1937.

were able to demonstrate traces of bismuth in the subarachnoid fluid of 2 of 3 dogs which had received 6 biweekly injections of 0.05 cc of iodobismutol per kilogram of body weight (the usual therapeutic dose for man) and daily during this period had ingested 10 cc of ethyl alcohol per kilogram. No bismuth could be found, however, in the subarachnoid fluid of 3 control animals which had received the same doses of iodobismutol but no alcohol. Further, in a more extensive series of experiments they compared the bismuth content of the blood, brain, cerebrospinal fluid and spinal cord of 8 dogs to which iodobismutol had been given biweekly in doses of 0.5 cc per kilogram until death occurred or for four weeks. Half the dogs also received 10 cc of ethyl alcohol daily, the remainder had none. The results are somewhat variable, owing in part at least to the technical difficulties of accurately estimating small quantities of bismuth in organic material. The authors feel, however, that they have shown that ingestion of alcohol under the circumstances of their experiments definitely increases the penetration of bismuth into the central nervous system.

Ko⁸⁹ describes two small groups of experiments in which he treated syphilitic rabbits by rubbing an ointment containing 2 per cent bismuth into the back. The results were extremely variable, but in the latter series a cure was obtained in 2 of 3 animals by 11 inunctions.

The group headed by Hanzlik have for many years been engaged in study of the chemistry and pharmacology of bismuth compounds for the treatment of syphilis, and in their most recent communications they⁹⁰ present a preliminary report concerning a new bismuth product. Sodium bismuthate, the compound which they employed, is not new, their contribution rests in having devised a method for taking it into solution to form what they term sodium bismuthate soluble, or sobisminol. The technic of preparation of the product consists essentially in dissolving sodium bismuthate in triisopropanolamine and with appropriate precautions adding propylene glycol and water to a final concentration of 3 per cent sodium bismuthate, 8 per cent triisopropanolamine and 50 per cent propylene glycol. The resulting solution is stable, it does not precipitate protein and by appropriate experiments it was shown to be well tolerated on intramuscular injection or oral administration by

89 Ko, H. The Effect of Inunction Treatment with Bismuth Organosol Salve in Experimental Rabbit Syphilis, *Lues Bull Soc japon de syph* **14** 22 (Dec) 1936, The Effect of Inunction Treatment with Bismuth Organosol Salve in Experimental Syphilis, *ibid* **15** 7 (April) 1937.

90 (a) Hanzlik, P. J. Sodium Bismuthate Soluble in Experimental Syphilis, *J Pharmacol & Exper Therap* **59** 328 (March) 1937. (b) Hanzlik, P. J., Lehman, A. J., and Richardson, A. P. Sodium Bismuthate Soluble. A New Product for Intramuscular and Oral Administration in the Treatment for Syphilis, a Preliminary Summary Report, *Am J Syph, Gonorr & Ven Dis* **21** 1 (Jan) 1937.

experimental animals and by both normal men and men with syphilis. In the treatment of rabbits with experimental syphilis the therapeutic index of sobisminol given by intramuscular injection was found to be not less than 10 and probably to be 15 or greater.^{90a}

The results of the observations on both normal human beings and those with syphilis treated with sobisminol^{90b} indicate that the drug is absorbed after either oral or intramuscular administration, that it is an effective antisyphilitic remedy and that its toxicity is low. Hanzlik believes, therefore, that sobisminol is entitled to extensive clinical trial, especially with regard to its suitability for the oral treatment or prophylaxis of syphilis.

Kolmer, Brown and Rule⁹¹ present a survey of the problems of evaluation of the oral administration of bismuth compounds and report the results of their investigations on the oral administration of bismuth and potassium tartrate to rabbits. They found that in spite of the high acidity of the stomach contents of the rabbit the drug was absorbed in therapeutically effective amounts.

"*Arsenical 190*"—Tatum and his collaborators⁹² present the results of an experimental and clinical study of arsenical 190,3-amino-4-beta-hydroxyethoxyphenylarsonic acid, which for administration is prepared as the sodium salt. Experimentally, the drug was found to be much superior to trypanasamide both in trypanosomiasis and in rabbit syphilis. Clinically, 128 patients with various forms of syphilis were given a total of 2,515 injections, usually of the optimum dose of 3 Gm. The drug was found to be effective in every stage of syphilis, but particularly in neurosyphilis, in which it appeared to be superior to trypanasamide. The incidence of toxic amblyopia was so high, however, that the drug is not recommended. In addition to the frequent occurrence of subjective reactions, in 16 patients objective changes developed in the visual fields or optic disks, 2 became blind and a third lost useful vision. The authors point out that this toxicity for the optic nerve is not unexpected, because of the existence of an amino group in the meta position to arsonic acid.

Neocyl—At the request of the Medical Research Council of Great Britain, Yorke and Murgatroyd⁹³ investigated the properties of sodium

91 Kolmer, J. A., Brown, H., and Rule, Anna M. The Oral Administration of Potassium Bismuth Tartrate in the Treatment of Experimental Syphilis of Rabbits, with a Note on the Gastric Chemistry of the Rabbit, *Am J Syph, Gonorr & Ven Dis* **21** 387 (July) 1937.

92 Tatum, A. L., Pfeiffer, C. C., Kuhs, M. L., Lorenz, W. F., and Green, J. T., Jr. A Study of the Sodium Salt of 3-Amino-4-Beta-Hydroxyethoxyphenylarsonic Acid in Experimental Trypanosomiasis and Syphilis and in Clinical Syphilis and Neurosyphilis, *J Pharmacol & Exper Therap* **59** 241 (March) 1937.

93 Yorke, W., and Murgatroyd, F. A New Arsenical for the Treatment of Syphilis and Trypanosomiasis, *Brit M J* **1** 1042 (May 23) 1936.

succinamylomethylamide-p-isonate, which is supplied in continental Europe under the name neocyl and which is being introduced in Great Britain as "crylaisan" In experimental animals the drug was found to be less toxic than tryparsamide and to possess somewhat greater trypanocidal activity By man the drug is well tolerated when administered in the same dose and in the same long courses customary in treatment with tryparamide In a large experience no visual disturbances or other serious reactions were observed The authors warn, however, that the chemical nature of the drug presents a risk of visual reactions Clinically, they found the action of the drug similar to that of tryparsamide in patients with neurosyphilis, but in contrast with tryparsamide, this drug possesses some effectiveness on other lesions of syphilis, both early and late

Mercury—Wright⁹⁴ presents a complete review of the use of mercury in syphilotherapy and concludes

Mercury must still be looked upon as a valuable syphilitic agent and probably will always retain a place in the ever growing list of antisyphilitic remedies

Acetarsone—Rosahn and Kemp⁹⁵ review the literature regarding the oral administration of acetarsone in the treatment of syphilis in human beings and experimental animals and report the results of their experience in treating 53 syphilitic rabbits They say

A review of the literature and our own investigations point to one outstanding conclusion, namely, that the toxicity of orally administered 3-acetyl-amino-4-hydroxyphenylarsonic acid as it is now manufactured is so variable as to preclude its use in the rabbit

This variability, they point out, may be either in the drug or in the animal and its biologic reactions The latter they think most likely Whatever it is, it renders the drug entirely unsuitable for use in the treatment of rabbit syphilis, and by analogy these authors argue that the drug is likewise unsuitable for use by human beings with syphilis

Rhodium—Jahnel⁹⁶ provides an interesting report of the use of rhodium compounds in the treatment of experimental syphilis in the rabbit Rhodium chloride or sodium rhodium chloride was utilized for intramuscular injection in doses of 0.05 or 0.1 Gm per kilogram of body weight The sodium salt was more effective, and especially after the larger dose dramatic healing of lesions occurred The compounds are of low toxicity, both were found to have a therapeutic index of more than 12.5 They may, however, produce local irritation at the site

94 Wright, C. S. Mercury in the Treatment of Syphilis, *Am J Syph, Gonorr & Ven Dis* **20** 660 (Nov) 1936

95 Rosahn, P. D., and Kemp, J. E. The Oral Administration of Stovarsol in the Treatment of Experimental Syphilis of the Rabbit, *Am J Syph, Gonorr & Ven Dis* **21** 180 (March) 1937

96 Jahnel, F. Ueber die Heilwirkung von Rhodiumverbindungen bei der experimentellen Syphilis und Framboesie, *Klin Wchnschr* **16** 657 (May 8) 1937

of injection Rhodium is expensive, but Jahnel feels that the experience is sufficiently encouraging to justify further experimental work. He does not feel, however, that there is yet enough information to warrant clinical trial of the rhodium compounds.

UNTOWARD EFFECTS OF TREATMENT

Cook and Wingo⁹⁷ seized the opportunity to determine the incidence of reactions to intravenous treatment of syphilis in the large experience of the Medical Department of the Navy and to compare the reaction rate for the year 1935 with that in the period since 1925. Over the entire period of eleven years there were given almost 1,000,000 doses of neoarsphenamine and from 20,000 to 40,000 doses each of arsphenamine, sulfarsphenamine and triparisamide. They found that reactions occurred at the rate of approximately 1 in 1,000 injections for all the drugs but triparisamide, with this drug there were only 2 reactions for 39,602 injections. The death rate was 1 per 37,101 injections for arsphenamine and 1 per 26,162 injections for neoarsphenamine.

Arsphenamine Dermatitis—Efforts to produce a phenomenon in experimental animals which is truly analogous to arsphenamine dermatitis in human beings continue, but with little success. Cormia⁹⁸ was able to produce a local sensitivity in the skin of the guinea-pig by endodermal injections of neoarsphenamine. This area would react to the intravenous injection of any trivalent arsenical compound but not to a pentavalent compound. He⁹⁹ further discovered that the reaction is not increased by the administration of staphylococcus toxin. Landsteiner and Jacobs¹⁰⁰ report the production of anaphylactic shock in guinea-pigs with or without the production of localized dermatitis at the point of the sensitizing injection. Frei¹⁰¹ makes the potentially important observation that guinea-pigs may not be sensitized to the arsphenamines before they are about 4 weeks old, during pregnancy or shortly thereafter.

Dennie and Miller¹⁰² report on 2 patients in whom adynamic ileus occurred as a complication of severe exfoliative dermatitis, with death

97 Cook, S. S., and Wingo, E. H. Toxic Effects of Arsenical Compounds as Administered in the United States Navy in 1935, with Special Reference to Arsenical Dermatitis, U. S. Nav. M. Bull. **34** 569 (Oct.) 1936.

98 Cormia, F. E. Experimental Arsphenamine Dermatitis, Canad. M. A. J. **34** 272 (March) 1936.

99 Cormia, F. E. Experimental Arsphenamine Dermatitis. Reaction to Arsphenamine in Normal Guinea Pigs and in Guinea Pigs Given Staphylococcus Toxin, Arch. Dermat. & Syph. **34** 107 (July) 1936.

100 Landsteiner, K., and Jacobs, J. Studies on the Sensitization of Animals with Simple Chemical Compounds. III. Anaphylaxis Induced by Arsphenamine, J. Exper. Med. **64** 717 (Nov.) 1936.

101 Frei, Wilhelm. Tierexperimenteller Beitrag zur Frage "Salvarsan und Saugling," Acta dermat.-venereol. **18** 396, 1937.

102 Denmie, C. C., and Miller, E. S. Arsphenamine Dermatitis. Paralytic Ileus and Perforation of the Intestine After Treatment with Arsphenamine, Arch. Dermat. & Syph. **35** 591 (April) 1937.

in both instances Muir¹⁰³ describes a patient in whom death occurred twenty-eight days after the third injection of arsphenamine. Three days after this injection toxic erythema developed which subsided, and thirteen days after the injection a bullous eruption developed which persisted. Autopsy revealed generalized toxic degeneration of the vital organs.

Tarras-Wahlberg¹⁰⁴ demonstrates that the histamine content of the blood is increased during arsphenamine dermatitis and varies directly with the severity of the dermatitis. McLachlan¹⁰⁵ enthusiastically advocates the use of calcium thiosulfate in the treatment of drug reactions of all sorts.

Erythema of the Ninth Day—Gordon¹⁰⁶ reports 2 cases in which the condition was typical of Milan's erythema of the ninth day and discussed the differentiation of "E 9," as he calls it, from the more usual form of arsphenamine dermatitis. The former comes on almost always on the ninth or tenth day after the first treatment, it is a scarlatiniform or morbilliform eruption which covers the face, the patient is not seriously ill and the eruption subsides within a few days. Further treatment with arsenicals is not contraindicated. The genesis of the condition is unknown, but Wainstein and Smelov¹⁰⁷ point out that it has many features in common with serum sickness.

Tryparsamide Dermatitis—Generalized dermatitis following the administration of tryparsamide is rare. Robinson,¹⁰⁸ however, reports on 1 patient who showed an ill defined generalized maculopapular eruption after tryparsamide therapy. The localized, so-called fixed exanthems are more commonly observed. Pillsbury¹⁰⁹ reports a unique

103 Muir, K. B. Vesiculobullous Dermatitis Following Administration of Arsphenamine. Report of a Case, *Arch Dermat & Syph* **35** 226 (Feb.) 1937.

104 Tarras-Wahlberg, B. Blood-Histamine in Salvarsan-Dermatitis, *Acta dermat-venereol* **18** 284, 1937.

105 McLachlan, A. E. W. Calcium Thiosulphate in the Treatment of the Complications of Arsphenamine and Bismuth Therapy in Syphilis, *J. Chemotherapy* **13** 127 (Jan.) 1937.

106 Gordon, H. Erythema of the Ninth Day, *Brit J Dermat* **48** 281 (June) 1936.

107 Wainstein, A., and Smelov, N. Sur la question de la symptomatologie, de la pathogenie et de la therapeutique des exanthemes precoces arsenobenzoliques—"erythèmes du neuvième jour" de Milan, *Ann de dermat et syph* **8** 215 (March) 1937.

108 Robinson, S. S. Dermatitis Due to Tryparsamide, *Arch Dermat & Syph* **34** 251 (Aug.) 1936.

109 Pillsbury, D. M. Fixed Arsenical Eruption. Sensitivity to Tryparsamide at Sites of Pigmentation Following Dermatitis Due to Silver Arsphenamine, *Arch Dermat & Syph* **34** 103 (July) 1936.

observation In his patient a fixed reaction to tryparsamide developed in cutaneous areas which four years before had been the site of a reaction to silver arsphenamine

Arsphenamine Jaundice—In an exhaustive discussion Soffer¹¹⁰ brings out that a clear understanding of the mechanism of postarsphenamine jaundice is no nearer today than it was two decades ago, with confusion in diagnosis constantly arising A study of the records of 158 patients with the condition, however, allowed some general conclusions Arsphenamine, he found, causes jaundice half again as frequently as neoarsphenamine, while the complication is rare after tryparsamide The white race is almost three times more likely to have posttreatment jaundice than Negroes, but the stage of the disease or the phase of the treatment seems to bear no influence In half of his patients jaundice developed within ten days after the last treatment, i e, it was "early," in the remainder it was "delayed" In a description of the clinical course of postarsphenamine jaundice Soffer emphasizes that the premonitory symptoms—malaise, nausea and sometimes vomiting—usually appear from four to eight days before icterus Ten of his patients had acute yellow atrophy of the liver, the remainder recovered Of these, 81 were subsequently given further arsenical treatment, with the development of a second attack of jaundice in 2 This presents no striking contrast to the gross incidence (0.87 per cent) of posttreatment jaundice in the group of patients from which his material was drawn

From this same group of patients who had recovered from postarsphenamine jaundice Campbell and Soffer¹¹¹ selected 27 in whom, as far as possible, the existence of any other cause of hepatic damage could be eliminated For these patients they performed a bilirubin excretion test for hepatic function from six months to fourteen years after the jaundice had subsided and at various periods in relation to treatment with arsenicals Ten of the 27 patients showed definite retention of bilirubin, 8 were on the borderline and the test for the remaining 9 gave normal results The authors point out that the retention of bilirubin in this series is not as great as that found with an identical technic by Soffer and Paulson¹¹² in patients who had recovered from catarrhal jaundice In addition, these authors performed the same test on 12 patients who had received moderate or relatively large amounts of anti-

110 Soffer, L. J. Postarsphenamine Jaundice, *Am J Syph, Gonorr & Ven Dis* **21** 309 (May) 1937

111 Campbell, A. D., and Soffer, L. J. The Results of the Bilirubin Test for Liver Function on Patients Recovered from Arsphenamine Jaundice, *Am J Syph, Gonorr & Ven Dis* **21** 420 (July) 1937

112 Soffer, L. J., and Paulson, Moses. Residual Hepatic Damage in Catarrhal Jaundice as Determined by the Bilirubin Excretion Test, *Arch Int Med* **53** 809 (June) 1934

syphilitic therapy but who had never been jaundiced. Two of them were found to show an abnormal retention of bilirubin.

Asteriades¹¹³ tested the urine for urobilinogen before each injection, a half hour afterward and sometimes at longer intervals for a group of 110 patients under regular treatment with arsphenamine. Transient and slight urobilinogenuria was found in 9 patients but in no instance was there other evidence of damage to the liver.

Graffar¹¹⁴ revives the arguments which favor the essential identity of postarsphenamine jaundice and catarrhal jaundice and reports the occurrence of posttreatment jaundice in 6 per cent of his series of 7,000 patients. This is much higher than the incidence reported by most observers.

Soffer¹¹⁵ studied the physicochemical changes in the blood of dogs in which hepatic damage had been produced by massive doses of arsphenamine. He regularly found a striking hemoconcentration, marked acidosis, due to increase in the quantity of lactic acid in the blood, and a considerable decrease in the chloride content of the blood serum. Somewhat less regularly he observed an increase in the inorganic phosphorus, potassium and magnesium contents of the blood serum. All the animals manifested evidences of nitrogen retention, and in 4 of the 6 hypoglycemia developed. Wien,¹¹⁶ working with mice, found that the mortality following a standard dose of neoarsphenamine was half again as great for those animals fed on grains as for those fed on bread and milk. Although he could find no difference in the glycogen content of the liver in the two groups of animals, this author feels sure that the conditions of carbohydrate metabolism determine the reaction of the body to the administration of arsenical drugs.

Tryparsamide Amblyopia—Sloan and Woods¹¹⁷ studied 16 patients who had visual disturbances after the administration of tryparsamide. In 15 of these the reaction was chronic in its development, but the remaining patient was blind three days after the first injection. The authors describe the characteristic defect in the visual fields, which is diagnostic of the condition, and emphasize that there is a marked tendency toward

113 Asteriades, M. Untersuchungen auf Urobilinogenurie nach Salvarsaneinspritzungen, *Dermat Wehnsch* **103** 1121 (Aug 15) 1936.

114 Graffar, M. Contribution a l'etude des ictères survenant au cours du traitement arsenical, *Presse med* **45** 661 (May 1) 1937.

115 Soffer, L. J. Blood Electrolyte Studies in Experimental Acute Liver Injury Produced by Arsphenamine in Dogs, *Proc Soc Exper Biol & Med* **35** 160 (Oct) 1936.

116 Wien, R. The Influence of Diet on the Toxicity of Mercurochrome and of Neoarsphenamine, *Quart J Pharm & Pharmacol* **9** 48 (Jan-March) 1936.

117 Sloan, L. L., and Woods, A. C. The Effect of Tryparsamide on the Eye. A Clinical Study of the Objective Ocular Reaction, *Am J Syph, Gonorr & Ven Dis* **20** 583 (Nov) 1936.

recovery if use of the drug is promptly and permanently discontinued. They conclude that the use of the drug carries with it little danger of permanent visual damage provided the optic nerve is previously normal. Wagener¹¹⁸ arrives at essentially the same conclusions, but he is not inclined rigidly to prohibit the use of tryparsamide for patients with disease of the optic nerve. Fine and Barkan¹¹⁹ also found that pretyparsamide examination of the ocular fundi and visual fields and a careful follow-up during the first course and periodically thereafter effectively safeguard the patient from the development of severe or permanent visual loss.

Intolerance to Tryparsamide—Schoch¹²⁰ describes 3 patients who presented an anomalous response to the administration of tryparsamide. Instead of producing the tonic effect which is so usually observed, treatment with the drug occasioned malaise, weakness, obvious impairment of the general state of being and loss of weight. All symptoms cleared up on suspension of treatment with the drug, only to reappear on its resumption. Miller and O'Donnell¹²¹ describe a patient who manifested toward tryparsamide an intolerance which simulated true allergic sensitization. This persisted for at least three years, although the patient received the trivalent arsenicals without reaction.

Medical Shock—In a report of 3 cases Weinberg¹²² calls attention to a little known and imperfectly understood syndrome which is best known as medical shock. All 3 patients presented the typical clinical picture of shock, which in 2 had come on immediately and in the third a few hours after the intravenous injection of neoarsphenamine. The condition persisted for several days. There were nausea and vomiting, marked hemoconcentration, evidences of nitrogen retention and an elevation of temperature. All 3 patients, however, recovered.

Granulocytopenia—Bock¹²³ describes a patient in whom severe granulocytopenia and necrotic pharyngitis developed after she received the eighth dose of neoarsphenamine. The notable feature is that eight

118 Wagener, Henry P. The Effect of Tryparsamide on the Optic Nerve, *Am J M Sc* **193** 286 (Feb) 1937

119 Fine, M., and Barkan, H. Prevention of Ocular Complications in Tryparsamide Therapy, *Am J Ophth* **2** 45 (Jan) 1937

120 Schoch, A. G. Intolerance to Tryparsamide, *Am J Syph, Gonorr & Ven Dis* **20** 408 (July) 1936

121 Miller, J. K., and O'Donnell, H. J. Sensitivity to Tryparsamide, *Arch Dermat & Syph* **35** 264 (Feb) 1937

122 Weinberg, T. Medical Shock Following Intravenous Therapy with Neoarsphenamine, *Am J Syph, Gonorr & Ven Dis* **21** 376 (July) 1937

123 Bock, H. E. Ueber einen bemerkenswerten Einzelfall symptomatischer Agranulocytose während einer Neosalvarsan-Bismogenol Kur, *Med Welt* **9** 1629 (Nov 9) 1935

months later she tolerated the further administration of neoarsphenamine without event

Purpura Haemorrhagica—Falconer and his collaborators¹²⁴ describe 2 patients in whom they had repeatedly produced purpura haemorrhagica by the administration of neoarsphenamine and in which the administration of mapharsen caused no untoward results

Hemorrhagic Encephalitis—Cormia¹²⁵ reports a case of hemorrhagic encephalitis following the administration of neoarsphenamine to a woman who was 23 years old and in the fifth month of pregnancy. He reviewed the literature on the subject and found reports of 135 cases. Forty-six of these patients were women and 34 were pregnant. Searching for some common factor which might suggest the etiology of the reaction, Cormia noted that almost all these patients had received doses of 0.45 Gm or more of neoarsphenamine. He concludes, therefore, that an overdose of arsenic is the chief factor in causing the syndrome and suggests that the maximum weekly dose of neoarsphenamine for pregnant women should not exceed 0.3 Gm. The speciousness of this reasoning is readily obvious.

Venous Spasm—One of the few troublesome features of the use of mapharsen is the occasional development of spasm of the vein into which the drug is injected, with attendant pain and sometimes consequent thrombosis. Schoch¹²⁶ brings out that cold compresses along the course of the vein bring relief and help to prevent thromboses. Heat, however, aggravates the condition.

THE PROPHYLAXIS OF SYPHILIS

In a general discussion of prophylaxis in the control of syphilis, Moore¹²⁷ brings out that the methods which may be applied fall into three groups: mechanical prophylaxis, chemical prophylaxis and chemotherapeutic prophylaxis. The first is best accomplished with the condom. Chemical prophylaxis should be performed at a prophylactic station under the direction of trained personnel. It consists in local cleansing and medication of the parts of the body which have been exposed. Chemotherapeutic prophylaxis is best accomplished by the regular injection

124 Falconer, E. H., Epstein, N. N., and Wever, G. K. *Purpura Haemorrhagica Following the Administration of Neoarsphenamine. The Reaction to Neoarsphenamine Compared with the Reaction to Mapharsen*, Arch Int Med **58** 495 (Sept.) 1936.

125 Cormia, F. E. *Haemorrhagic Encephalitis from Neoarsphenamine in Pregnancy*, Canad M A J **35** 610 (Dec.) 1936.

126 Schoch, A. G. *Treatment of Venous Spasm Resulting from Injection of Mapharsen or Arsphenamine*, Arch Dermat & Syph **34** 1031 (Dec.) 1936.

127 Moore, J. E. *Prophylaxis in the Control of Syphilis*, South M J **30** 149 (Feb.) 1937.

tion of a bismuth compound, but the potentialities of acetarsone by mouth in this field should be further investigated

Chemical Prophylaxis—Hood¹²⁸ and Esquier¹²⁹ bring out that chemical prophylaxis as enforced on troops or seamen at a central station breaks down primarily because the prophylaxis is taken too long after the initial exposure. This point has been long recognized and may in a large measure be obviated by education.

Astwazaturow and Juschkow¹³⁰ tested the effect of a large number of chemical and biologic agents on the motility of a virulent strain of *S. pallida*. They discovered that a 1:2,000 solution of several mercury salts, 1 per cent phenol, ethyl alcohol of more than 60 per cent concentration, potassium soap lather and hydrogen peroxide are effective in destroying spirochetes. Sodium soap lather and eau de Cologne (perfumed spirit N. F.) are not. In general, throughout a large series of substances which they tested the spirochete was found to be susceptible to those which are acid in reaction and to be resistant to those which give an alkaline reaction.

Chemotherapeutic Prophylaxis—In spite of the encouraging results reported by Sonnenberg¹³¹ and others, as previously mentioned,¹ on the bismuth prophylaxis of syphilis in selected groups, especially prostitutes, the method has not gained favor. Rabut,¹³² Lacassagne and Lebeuf¹³³ and Gaté and Cuilleret¹³⁴ present a symposium on the subject, in which they agree that the method is not practically applicable and that there are many theoretical objections to its use.

THE TREATMENT OF EARLY SYPHILIS

Methods—Stokes and Usilton¹³⁵ subject the League of Nations investigation of the treatment of early syphilis, which was previously

128 Hood, A. The Prevention of Venereal Disease with Special Reference to Preventive Ablution Centers, *J. Roy. Army M. Corps* **48** 390 (June) 1937.

129 Esquier, A. Prevention of Syphilis, *Bull. Soc. franç. de dermat. et syph.* **43** 1173 (June) 1936.

130 Astwazaturow, K. R., and Juschkow, P. D. Ueber die Standhaftigkeit der blassen Spirochaten, *Acta dermat.-venereol.* **17** 43, 1936.

131 Sonnenberg, E. Neuf ans de traitement préventif bismuthique de la syphilis, *Bull. Acad. de med., Paris* **114** 374 (Nov. 5) 1935.

132 Rabut, R. A propos du traitement préventif de la syphilis, *Bull. Soc. franç. de dermat. et syph.* **43** 1186 (June) 1936.

133 Lacassagne, J., and Lebeuf, F. Considerations sur la metallo-prévention chez les prostituées, *Bull. Soc. franç. de dermat. et syph.* **43** 1189 (June) 1936.

134 Gaté, J., and Cuilleret, P. A propos de la metallo-prévention par le bismuth, *Bull. Soc. franç. de dermat. et syph.* **43** 1191 (June) 1936.

135 Stokes, J. H., and Usilton, L. J. Continuous and Intermittent Treatment for Early Syphilis. A Critical Review of the American and the League of Nations' Investigation, with Additional Evaluations, *Arch. Dermat. & Syph.* **35** 377 (March) 1937.

reviewed,¹³¹ to a critical resurvey and bring out some interesting additional information. They find that Martenstein's¹³⁶ report actually allows no critical comparison between the results obtained by continuous and those obtained by intermittent treatment. This is because of the fact that while patients were counted as having had continuous treatment only if they actually had been so treated, many patients were considered as having had intermittent treatment when the treatment really had been haphazard. These authors therefore went over the material of the Cooperative Clinical Group and discovered that whereas no difference between the two methods could be demonstrated during the first three months of treatment, after that period had passed the system of continuous treatment could be shown to produce significantly better results, with no more reactions. Sixty-eight per cent of the group of patients who had received continuous treatment had attained a negative reaction to serologic tests for syphilis at the end of a year. In the group who had only a month's rest from treatment during the first year, however, only 40 per cent had been so fortunate.

Moore¹³⁷ recapitulates the evidence which favors the continuous method of treatment and brings out that the proper treatment of patients with early syphilis is of importance not only to the patient and the public health but also to the public expense. This is because it is much cheaper to treat a patient for early syphilis than to care for him when he is broken down with late lesions of the disease. By and large, however, patients with early syphilis are not being properly treated. The reason for this lies, he says, in part within the biology of the disease, with its high incidence of symptomless infection, in part with the laity and in part with physicians. The fault which lies with the laity is ignorance and, worse, unwillingness to learn. The fault of the physicians is threefold. They have not taken the lead in education of the laity, they do not apply modern methods for early diagnosis and, though adequate methods of treatment have been developed, they do not apply them.

Rosahn¹³⁸ and an editorial commentator¹³⁹ deplore the abandonment of tried methods of treatment of early syphilis for the untried methods of fever therapy or of treatment with drugs administered by mouth.

136 Martenstein, cited by Padget and Moore^{1b}

137 Moore, J. E. The Continuous Method of Treatment of Early Syphilis, *Ann Int Med* **10** 30 (July) 1936

138 Rosahn, P. D. The Treatment of Syphilis. Modern Methods Versus Artificial Fever and Orally Administered Bismuth Preparations, *J Chemotherapy* **13** 49 (July) 1936

139 The Oral Medication of Syphilis, editorial, *Am J Syph, Gonorr & Ven Dis* **21** 456 (July) 1937

The former topic was made the subject of extensive comment in a previous review,^{1b} to this Rosahn adds the weight of another opinion. Concerning the treatment of syphilis by oral medication the editorial comment concludes

It is felt by many that there is little place at present for new drugs in the treatment of syphilis unless they show promise of superiority to the most efficient of those in use at the present time. This does not mean that efforts to evolve new preparations, whereby the treatment of syphilis would become shorter, less expensive, and more convenient, should not continue. However, before any preparation is offered for general use in the treatment of syphilis, no matter how it is to be administered, it must be preceded by the same careful experimental and clinical study which preceded the introduction of arsphenamine. There is insufficient evidence that the drugs proposed for the oral treatment of syphilis have met these requirements.

Results—In addition to the results of the studies by the Cooperative Clinical Group and the Health Organization of the League of Nations which have been previously discussed,^{1b} there now is accumulating an impressive body of independently conducted studies which seek even more detailed and comprehensive evaluation of the results of the treatment of patients with early syphilis. Milian and his collaborators¹⁴⁰ were able in 1935 to follow 375 of the patients with early syphilis who had been treated at the St. Louis Dispensary between 1922 and 1924, thus giving a ten year follow-up period. All these patients had received treatment which would be considered minimal by the standards of the Cooperative Clinical Group. Of the 375 patients, 29.8 per cent had had a recurrence or relapse, but 243, or 64.8 per cent, were apparently well at the end of ten years. After a shorter follow-up period Nicastro¹⁴¹ found that among 875 patients who had been treated at Palermo during the past five years the incidence of late syphilis was strictly related to the amount of treatment which the patient had had for early syphilis.

In a unique study Rosahn¹⁴² investigated the effect of inadequate treatment of patients with early syphilis on the final outcome of the disease process. His study is based on the data for 409 patients who had received less than 20 injections of an arsphenamine preparation and of heavy metal within a year during the first two years after the onset of the disease. He was able to demonstrate the superiority of continuous over intermittent or irregular treatment and to show that there was a relation between the amount of treatment which the patient had received and the eventual result. In this group there were 134 (32.8

140 Milian, G., Perin, L., and Lafourcade. Resultats éloignes du traitement de la syphilis, *Rev. franç. de dermat. et de venerol.* **12** 511 (Nov.) 1936.

141 Nicastro, A. La sorte lontana dei sifilitici in rapporto alle cure iniziali, *Gior. ital. di dermat. e sif.* **76** 1477 (Dec.) 1935.

142 Rosahn, P. D. The Inadequate Treatment of Early Syphilis, *Am. J. M. Sc.* **193** 534 (April) 1937.

per cent), most of whom were observed more than two years after the cessation of treatment for whom the result of treatment was classified as satisfactory. The author points out, however, that whereas a normal cerebrospinal fluid presents to these patients a virtual guarantee against the subsequent development of neurosyphilis, they face an unknown and unmeasurable hazard in the form of the later development of cardiovascular syphilis.

CLINICAL PHENOMENA IN EARLY SYPHILIS

Extragenital Primary Syphilis—The large number of patients with late syphilis who are able to give no history suggesting the noting of a genital primary lesion provides a constant stimulus for interest in the incidence of extragenital infection. It is axiomatic that many, perhaps a majority, of the extragenital primary lesions go unrecognized, but a study such as that of Schmidt¹⁴³ serves as a reminder that primary syphilis may occur, as Stokes says, anywhere but on the teeth and nails. During the ten year period ending in 1935 this author observed 305 men and 66 women with primary syphilis, which was extragenital in localization in 65 per cent of the former and in 15.5 per cent of the latter. The majority of the extragenital lesions were about the mouth, with the tonsil the most common site.

Reports of individual cases confirm the ubiquity of primary syphilis. Perkins¹⁴⁴ and Fox¹⁴⁵ describe the case of an 18 year old girl who had a chancre of the bulbar conjunctiva. The mode of infection was not clear. Weissenbach and his collaborators¹⁴⁶ report the occurrence of a chancre in the right nostril.

The Diagnosis of Early Syphilis—Photinos¹⁴⁷ observes that the diagnosis of seronegative primary syphilis by dark field examination may be greatly impeded by the inaccessibility of the lesion under suspicion, by the fact that the patient has applied to it spirocheticidal medication or by the fact that it is so old that organisms have disappeared from the surface. He recommends therefore the dark field examination of material obtained by gland puncture as a routine procedure and

143 Schmidt, W. Statistisch-klinische Betrachtungen über die von 1926 bis 1935 beobachteten Erkrankungen an Lues I und Lues II, *Dermat Ztschr* **73** 285 (June) 1936.

144 Perkins, O. P. Chancre of the Conjunctiva. Report of a Case, *Arch Ophth* **17** 381 (Feb.) 1937.

145 Fox, H. Chancre of the Bulbar Conjunctiva, *Arch Dermat & Syph* **35** 553 (March) 1937.

146 Weissenbach, Basch and Le Baron. Chancre syphilitique fissuraire de la narine, *Bull Soc franç de dermat et syph* **43** 1259 (June) 1936.

147 Photinos, P. La recherche du treponème par la ponction des ganglions: méthode de Hoffmann modifiée par Gougerot, *Ann d mal ven* **31** 481 (July) 1936.

reports the impressive results of his own experience. No patient for whom gland puncture gave negative results subsequently was proved to have had primary syphilis. There were in his series 104 patients for whom gland puncture gave positive results. In 36 of these patients spirochetes could be demonstrated in material from the primary lesion. For 46 of the remaining 68, for whom dark field examination of material from the suspected primary lesion could not be carried out for technical reasons or for whom negative results were obtained, the serologic test for syphilis gave a positive reaction. For the remaining 22, or 21 per cent of the entire group, however, the diagnosis of seronegative primary syphilis was made by gland puncture alone.

Carley¹⁴⁸ brings up again the rôle of gonorrhea in masking the lesions of early syphilis when the two diseases coexist. From the clinic of the United States Public Health Service in Hot Springs, Ark., he was able, by routine serologic follow-up of patients with gonorrhea, to detect 8 fresh infections with syphilis. Unfortunately, he does not indicate the total number of patients who were followed in this study.

TRANSFUSION SYPHILIS

No one pretends that the transmission of syphilis by the transfusion of blood is ever to be justified. Until the immediate past, however, those who had participated in or were aware of an instance of this regrettable tragedy were so secretive that the medical literature contains no reliable estimate either of the incidence of transfusion syphilis or of the variety of human error most frequently responsible for its production. More recently observers have become bolder. Willis¹⁴⁹ reports the instance of a woman who acquired syphilis from a donor who was known to have syphilis. Because he had had 6 intravenous treatments and had manifested a negative reaction to a serologic test for syphilis, he was thought to be a safe donor. In the recipient, however, syphilis developed. Tasaki¹⁵⁰ reports a similar case.

Gilman¹⁵¹ presents an exhaustive discussion of the subject. He points out that careful examination of donors is desirable but that if a choice must be made between an unknown donor and one known to have late syphilis, the latter is probably safer.

148 Carley, P. S. Infection with Syphilis Masked by Gonorrhea, *Ven Dis Inform* **18** 21 (Feb) 1937.

149 Willis, M. W. Transfusion Syphilis, *New York State J Med* **37** 60 (Jan) 1937.

150 Tasaki, K. Syphilis Transmitted by Blood Transfusion, *J Orient Med* **25** 54 (Sept) 1936.

151 Gilman, R. L. Syphilis and Transfusion, *Indian J Ven Dis* **2** 176 (Sept) 1936.

REINFECTION WITH SYPHILIS

Reinfection with syphilis is troublesome to prove. It does occur, however, and Millspaugh¹⁵² reports 18 instances which he discovered among the 252 records of cases of syphilis on file at the Naval Air Station in Pensacola, Fla. This author was impressed primarily by the significance of reinfection as signaling the biologic "cure" of the first infection, and carefully quantitated the amount of treatment which each patient had received for the first infection. He found that on the average each man had received 27.7 injections of neoarsphenamine, 16.2 injections of a bismuth compound and 10 injections and 31.1 injections of mercury.

Attilio¹⁵³ reports a single case of reinfection which seems beyond cavil, and Sézary¹⁵⁴ describes a patient who clearly seems to have sustained three infections with syphilis.

LATE SYPHILIS

Most of the recent literature on late syphilis consists of reports of individual cases or of small groups. Only a few of these are of sufficient interest to warrant inclusion here. Among the more general discussions, da Silva Mello¹⁵⁵ presents an unconvincing and completely undocumented attempt to define chronic syphilitic nephritis.

McNamara¹⁵⁶ and White and Gaines¹⁵⁷ discuss syphilitic orchitis in the course of general considerations of the causes for testicular swelling. Both emphasize the necessity for the greatest care in the differential diagnosis between syphilis, tuberculosis and malignant disease. Keyes¹⁵⁸ reports the case of a man 60 years of age who was known to have syphilis and from whom a prostatic mass was removed. Microscopic study showed that it might well be gummatous.

152 Millspaugh, J. O. An Analysis of Eighteen Syphilitic Reinfections, *U S Nav M Bull* **35** 240 (April) 1937.

153 Attilio, A. Un caso di presumibile reinfezione sifilitica, *Gior ital di dermat e sif* **77** 751 (Oct) 1936.

154 Sézary, A. Trois contaminations syphilitiques chez un même sujet en 12 ans, *Bull Soc franç de dermat et syph* **44** 349 (Feb) 1937.

155 da Silva Mello, A. Die chronischen syphilitischen Nephritiden als eine selbständige Gruppe von Nierenkrankheiten, *Deutsche med Wchnschr* **62** 70 (Jan 10) 1936.

156 McNamara, E. P. Syphilis, Tuberculosis and Malignant Tumors of Testis. Pathology and Differential Diagnosis, *J Iowa M Soc* **27** 28 (Jan) 1937.

157 White, E. W., and Gaines, R. B. The Clinical Significance and Rationale of Management of Testicular Swellings, *J A M A* **108** 1227 (April 10) 1937.

158 Keyes, E. L. Granuloma of the Prostate Possibly Due to Syphilis, *Am J Syph, Gonorr & Ven Dis* **20** 418 (Oct) 1936.

The most dramatic case of the year is reported by Wilhelm and Scholtz¹⁵⁹ These authors supply postmortem photographs which show an unbelievably extensive ulceration, with destruction of tissue about the head, neck and upper portion of the body The process had been developing for four years from an original lesion in the mouth Fortunately, the authors were able to recover *S. pallida* from the lesion The illustrations must be seen to be appreciated

Syphilis of the Stomach—Carter,¹⁶⁰ in a general discussion of the roentgenologic diagnosis of gastric syphilis, brings out the characteristics which warrant a therapeutic test for syphilis before the institution of more radical measures The most important of these are, in a patient with syphilis, the presence of an annular prepyloric constriction in the absence of a palpable mass, absence of peristalsis but some flexibility on manipulation, and minor symptoms Widen¹⁶¹ and Fenster¹⁶² report individual cases in which the diagnosis of syphilis of the stomach was carefully established Rentschler¹⁶³ reports that 1 of a group of 100 patients with surgical conditions of the stomach had gastric syphilis with duodenal obstruction

CARDIOVASCULAR SYPHILIS

Incidence of Cardiovascular Syphilis—Among a group of 485 seamen with heart disease Arenberg¹⁶⁴ found that 130 (27 per cent) had syphilis and that 57 (12 per cent) were suffering from outspoken cardiovascular syphilis

From a study of necropsy records Nickel¹⁶⁵ found that some lesion of syphilis had been recorded for 1,203 (6 per cent) of the 20,040 patients examined post mortem in Dusseldorf from 1907 through 1933 In the first period, 1907 through 1915, 75 per cent of the patients with anatomically demonstrable lesions of syphilis manifested syphilis of the aorta During the next decade the observed incidence of aortic involve-

159 Wilhelm, L. F. X., and Scholtz, J. R. Extensive Ulcerations in Wholly Untreated Syphilis, *Arch. Dermat. & Syph.* **34** 242 (Aug.) 1936

160 Carter, R. A. Non-Carcinomatous Tumors of the Stomach, *Radiology* **28** 301 (March) 1937

161 Widen, A. A Case of Visceral Syphilis Operated upon Twice—with an Interval of Twenty-Six Years—Because of Suspected Cancer of the Stomach, *Acta dermat.-venereol.* **18** 216, 1937

162 Fenster, E. Syphilitischer Schrumpfmagen, *Arch. f. klin. Chir.* **187** 705 (Jan. 25) 1937

163 Rentschler, C. B. Surgical Lesions of the Stomach. Immediate and Late Results in One Hundred Consecutive Cases, *Am. J. Surg.* **35** 529 (March) 1937

164 Arenberg, H. Heart Disease Among Seamen, *Am. Heart J.* **13** 197 (Feb.) 1937

165 Nickel, H. Statistische Untersuchungen über die Häufigkeit der Lues am Obduktionsmaterial, *Klin. Wchnschr.* **15** 121 (Jan. 25) 1936

ment rose to 85 per cent of the group with syphilitic lesions, and in the period from 1926 through 1933, it rose again to 89 per cent. It must be emphasized, however, that these figures deal with the incidence of aortic involvement in patients with some lesion of syphilis, aortic or otherwise, which could be observed at necropsy. There is sad need for similar studies of all patients for whom a clinical diagnosis of syphilis has been made, especially those with latent syphilis who have died from other causes.

In a group of 200 Negroes with sufficiently severe forms of neurosyphilis to require institutionalization, Tildon¹⁶⁶ found that 38 had serious syphilitic disease of the cardiovascular system and that 27 others were suffering from other serious cardiovascular disorders. Cole and his colleagues¹⁶⁷ discovered that 10 per cent of the 6,253 patients with late syphilis included in the study made by the Cooperative Clinical Group manifested cardiovascular syphilis either when first seen or subsequently.

The Diagnosis of Cardiovascular Syphilis—Kemp and Cochems¹⁶⁸ had the unique opportunity to study posterior-anterior teleroentgenograms which had been made by an identical technic for 600 nonsyphilitic persons and 1,000 patients with syphilis. The former represented a fair sample of the population, the latter group was not weighted in either direction, since the incidence of cardiovascular syphilis was essentially the same (12.7 per cent)¹⁶⁹ as that noted by others who have studied large groups of patients with syphilis. The teleroentgenograms were all remeasured according to the method of Vaquez and Bordet, and the clinical record of each patient was searched for relevant data. They found:

2 The increased widening of the supracardiac shadow resulting from essential hypertension and arteriosclerosis with or without hypertension was the same in nonsyphilitic as in syphilitic individuals without syphilitic heart disease.

3 The increase in the width of the aortic arch shadow as a result of advancing age was the same in both syphilitic and nonsyphilitic individuals without heart disease.

166 Tildon, T. T. Cardiovascular Disease Complicating Neurosyphilis Among Negro Veterans, *M. Bull. Vet. Admin.* **13** 144 (Oct.) 1936.

167 Cole, H. N., Usilton, L. J., Moore, J. E., O'Leary, P. A., Stokes, J. H., Wile, U. J., Parran, T., Jr., and McMullen, John. Cooperative Clinical Studies in the Treatment of Syphilis. The Effect of Specific Therapy on the Prophylaxis and Progress of Cardiovascular Syphilis. *J. A. M. A.* **108** 1861 (May 29) 1937.

168 Kemp, J. E., and Cochems, K. D. Studies in Cardiovascular Syphilis. I. Teleroentgenography in the Diagnosis of Early Syphilitic Aortitis, a Comparison of Findings in One Thousand Syphilitic and Six Hundred Nonsyphilitic Individuals, *Am. Heart J.* **13** 297 (March) 1937.

169 Cochems, K. D., and Kemp, J. E. Studies in Cardiovascular Syphilis. II. The Incidence of Syphilitic Aortitis, a Study of One Thousand Syphilitic Individuals, *Am. J. Syph., Gonorr. & Ven. Dis.* **21** 282 (May) 1937.

4 Only 59 per cent of the patients with clinically recognizable syphilitic aortitis showed teleroentgenographic evidence of aortic dilatation

The authors therefore conclude that there is no evidence that the diagnosis of uncomplicated syphilitic aortitis can be made by teleroentgenography alone. Fluoroscopy and careful clinical evaluation of symptoms and physical signs are essential.

In a second communication these authors¹⁶⁹ report the distribution of the incidence of cardiovascular syphilis in their group of 1,000 syphilitic patients. The gross incidence of cardiovascular syphilis was 12.7 per cent, but it was 10.8 per cent for the women and 13.4 per cent for the men. These figures, they point out, are in essential agreement with the findings of Bruusgaard and of Turner. They are, however, sharply in contrast with the findings reported by Maynard and his colleagues,¹⁷⁰ who discovered cardiovascular syphilis in 41.9 per cent of a group of 346 persons with syphilis. This difference, Kemp and Cochems think is unquestionably due to differences in the criteria for the diagnosis of early syphilitic aortitis which were employed. They made the diagnosis of uncomplicated aortitis only on the demonstration of at least three diagnostic criteria, whereas Maynard and his group made the diagnosis solely by the teleroentgenographic demonstration of "increased aortic width."

Padget and Moore¹⁷¹ reviewed the literature regarding roentgenologic methods in the diagnosis of uncomplicated syphilitic aortitis and conclude

From examination of the evidence it seems clear that teleroentgenography in the posteroanterior position offers no reliable aid toward the early diagnosis of uncomplicated syphilitic aortitis, and the usefulness of other methods of examination is far from established. The studies of various workers, particularly Fray, regarding the use of the left anterior oblique position for teleroentgenography, preceded and supplemented by fluoroscopy, seem the most promising and should be further elaborated, and the roentgenologic findings should be closely compared with clinical and necropsy data. The preferable method of investigation would be by serial roentgenographic studies of groups of normal and diseased individuals, at periodic intervals over a lifetime, ending with necropsy confirmation of the presence or absence of aortic disease.

From a study of large numbers of roentgenokymograms Scott and his co-workers¹⁷² conclude that aortic regurgitation produces a perfectly

170 Maynard, E. P., Jr., Curran, J. A., Rosen, I. T., Williamson, C. G., and Lingg, C. Cardiovascular Syphilis. Early Diagnosis and Clinical Course of Aortitis in Three Hundred and Forty-Six Cases of Syphilis, *Arch. Int. Med.* **55**: 873 (June) 1935.

171 Padget, P., and Moore, J. E. The Roentgenologic Diagnosis of Syphilitic Aortitis, *Am. J. Syph., Gonorr. & Ven. Dis.* **21**: 199 (March) 1937.

172 Scott, W. G., and Moore, S. Roentgenokymography. Its Clinical and Physiological Value in the Study of Heart Disease, *Ann. Int. Med.* **10**: 306 (Sept.) 1936. Scott, W. G., Moore, S., and McCordock, H. A. Roentgenkymographic Studies of Cardiac Conditions, *Radiology* **28**: 196 (Feb.) 1937.

diagnostic roentgenokymographic tracing. Characteristic changes were found, however, in only about half of a group of patients whose condition had been diagnosed clinically as uncomplicated syphilitic aortitis. These changes, too, were indistinguishable from those seen in patients with arteriosclerosis. The picture produced by aneurysm of the aorta was found to be even less distinctive.

The Rôle of Occupation in the Genesis of Cardiovascular Syphilis—Cochems and Kemp¹⁷³ investigated the relation between occupation and incidence of cardiovascular syphilis in the 749 men among the 1,000 patients with syphilis who had been dealt with in other studies.¹⁷⁴ They found the incidence of syphilitic aortic disease to be greater among persons of intermediate and heavy occupational pursuits (141 per cent) than among those who followed sedentary occupations (87 per cent). The incidence of uncomplicated aortitis, however, was greater among persons who followed the lighter occupations, whereas aneurysm and aortic regurgitation occurred much more commonly among those who followed occupations which demanded a certain amount of physical exertion.

General Considerations—Willius¹⁷⁵ and Goeckerman and Wilhelm¹⁷⁶ present general discussions of the problems of cardiovascular syphilis, the latter placing particular emphasis on the practical aspects of management of the patient.

Bruenn, Turner and Levy¹⁷⁷ correlate the clinical cardiac symptoms and autopsy observations for 476 patients, 64 of whom had syphilitic aortitis. Pain had not been noted by any of the patients who did not manifest encroachment on the coronary ostia. They conclude, therefore, that pain is not a part of the picture of uncomplicated aortitis.

Andersen and McCutchan¹⁷⁸ reiterate the observation that disturbance of cardiac rhythm is rare in patients with cardiovascular syphilis.

173 Cochems, K. D., and Kemp, J. E. Studies in Cardiovascular Syphilis. III. The Effect of Occupation upon the Incidence and Type of Syphilitic Aortitis, *Am J Syph, Gonorr & Ven Dis* **21** 408 (July) 1937.

174 Kemp and Cochems¹⁶⁸ Cochems and Kemp¹⁶⁹

175 Willius, F. A. Cardiovascular Syphilis. *Mississippi Doctor* **15** 1 (June) 1937.

176 Goeckerman, W. H., and Wilhelm, L. F. X. Cardiovascular Syphilis, with Special Reference to Its Practical Management, *Am J Syph, Gonorr & Ven Dis* **20** 412 (July) 1936.

177 Bruenn, H. G., Turner, K. B., and Levy, R. L. Notes on Cardiac Pain and Coronary Disease. Correlation of Observations Made During Life with Structural Changes Found at Autopsy in Four Hundred and Seventy-Six Cases, *Am Heart J* **11** 34 (Jan) 1936.

178 Andersen, M. C., and McCutchan, G. R. One Thousand Patients with Heart Tracings, *Nebraska M J* **21** 128 (April) 1936.

Syphilitic Myocarditis—Norris¹⁷⁹ has long maintained that syphilis attacks the myocardium much more frequently than is generally conceded. The failure to demonstrate spirochetes in the myocardium does not, he says, necessarily imply that they are absent. In his opinion myocardial syphilis should be suspected in any patient with early syphilis who presents cardiac complaints, and he feels that it would be a great step forward if physicians would worry more about the heart and less about the chancre of patients with early syphilis. He describes 3 patients, 1 with associated aortic regurgitation, who died of myocardial failure. In each case Weller was able to demonstrate spirochetes in the myocardium.

Reifenstein¹⁸⁰ reviews the literature on syphilitic myocarditis which has accumulated since 1918 and reports a case. His patient was a white man 26 years of age who had had syphilis for seven years. Three months before the final illness a cutaneous eruption, similar to one which he had noted two years after the original infection, appeared. Treatment for syphilis was begun but was abandoned two weeks before the acute illness began. He presented the clinical picture of acute myocardial infarction and a papulosquamous eruption, the nature of which was not clear. Death occurred seventeen days after the onset, and necropsy revealed acute granulomatous myocarditis with multiple caseating foci. These were histologically typical of gumma.

Taussig and Oppenheimer¹⁸¹ report a somewhat similar instance in a child 6 years of age who had sickle cell anemia and tuberculosis and who had acquired syphilis by transfusion. Recurrent secondary syphilis developed two or three days after the ninth dose of sulfasphenamine, and the child died within two weeks of cardiac failure. Necropsy revealed granulomatous myocarditis the appearance of which was compatible with a diagnosis of gumma.

Syphilitic Aortitis and Bacterial Endocarditis—In reviewing the records of 193 cases of bacterial endocarditis Smith¹⁸² found 3 in which there had been coexistent syphilitic aortitis. Two were from the group of 22 cases in which the condition was classified as acute bacterial endocarditis, the third was found among the 171 cases in which the disease had been of the more usual subacute variety.

179 Norris, J. C. Syphilis of the Myocardium and Coronary Arteries, J. A. M. A. **108** 169 (Jan. 16) 1937.

180 Reifstein, E. C. Acute Gummatous Myocarditis Simulating Acute Myocardial Infarction, Ann. Int. Med. **10** 241 (Aug.) 1936.

181 Taussig, H. B., and Oppenheimer, E. H. Severe Myocarditis of Unknown Etiology, Bull. Johns Hopkins Hosp. **59** 155 (Sept.) 1936.

182 Smith, F. J. The Co-Existence of Syphilis of the Aorta and Bacterial Endocarditis, Internat. Clin. **2** 1, 1937.

The Effect of Treatment on the Histologic Appearance of Syphilitic Aortitis—Hood and Mohr¹⁸³ compared the microscopic pathologic appearance of the aorta in two groups each of 17 patients. The patients of one group were known to have received at least the equivalent of eight months of continuous antisyphilitic therapy. The second group was made up of patients known to have received no antisyphilitic treatment. The only differences observed in the microscopic appearance of the aorta were relatable to the duration of the syphilitic infection, in smaller groups in which age and duration of infection were strictly comparable, the histologic pictures of the aortic wall were practically identical, whether the patient had received treatment or not.

Dissecting Aneurysm—Sherman¹⁸⁴ presents a monumental contribution on dissecting aneurysm, which is based on a study of 300 cases. Seventeen of these he had personally observed, the remainder had been reported on in the literature. He says

Syphilitic mesaortitis was present in my case No. 2 (F, 39). This is unusual, as absence of frankly syphilitic disease of the aorta is generally regarded as one of the outstanding differences between ordinary aneurysm and dissecting aneurysm. But in 12 others of the reported cases syphilis was deemed to be present. Further, in 8 case reports there are suggestive descriptions, but no microscopic examination. (He concludes therefore that) ordinarily syphilis is not a prominent factor in the aetiology of dissecting aneurysms.

Glendy, Castleman and White¹⁸⁵ arrive at the same conclusions from a study of the literature and of their 19 cases. Contrariwise, Peery¹⁸⁶ feels that 1 of his 5 patients certainly and another probably were syphilitic. He points out, however, that even if a patient has syphilis, the usual factors must operate before a dissecting aneurysm can form.

Intracranial Aneurysm—Dial and Maurer¹⁸⁷ report that in only 2 of their group of 13 patients with intracranial aneurysm was syphilis the responsible factor. In 1 of these there were multiple syphilitic aneurysms of the right middle cerebral artery, the other had syphilitic aneurysms of both internal carotid arteries.

183 Hood, B. J., and Mohr, C. F. The Microscopic Pathologic Appearance of the Aorta in Treated and Untreated Patients with Syphilitic Aortitis, *Am J Syph, Gonorr. & Ven. Dis.* **21** 177 (March) 1937.

184 Sherman, T. Dissecting Aneurysms, Medical Research Council, Special Report Series, no. 193, London, His Majesty's Stationery Office, 1934.

185 Glendy, R. E., Castleman, B., and White, P. D. Dissecting Aneurysm of the Aorta. A Clinical and Anatomical Analysis of Nineteen Cases (Thirteen Acute), with Notes on the Differential Diagnosis, *Am Heart J.* **13** 129 (Feb) 1937.

186 Peery, T. M. Dissecting Aneurysm of the Aorta, with a Report of Five Cases, *Am Heart J.* **12** 650 (Dec) 1936.

187 Dial, D. L., and Maurer, G. B. Intracranial Aneurysms. Report of Thirteen Cases, *Am J Surg.* **35** 2 (Jan) 1937.

NEUROSYPHILIS

Incidence of Neurosyphilis—Matras¹⁸⁸ examined the cerebrospinal fluid of 721 patients with early syphilis before the institution of treatment. In 95 instances (13 per cent) a positive result was obtained. The degree of abnormality was striking, however, only in patients with secondary syphilis.

In two studies from the Boston Psychopathic Hospital Moore and Merritt¹⁸⁹ discuss the rôle played by neurosyphilis in the production of mental disease. They found that when corrections were made for the number of patients found to be "not psychotic" and for the number of patients readmitted syphilis of the nervous system was responsible for the mental disease in 9.3 per cent of their patients. In 94 per cent of this group the neurosyphilitic disease was dementia paralytica.

In the course of the routine postmortem examination of the cranial contents of 5150 patients Peers¹⁹⁰ reports that one hundred and eighty-eight tumors of the central nervous system were discovered. Three were gummas.

The Genesis of Neurosyphilis—The studies of the Cooperative Clinical Group, with O'Leary¹⁹¹ as spokesman, clearly show the effect of discontinuity of treatment in promoting the development of involvement of the neuraxis. Of the group of patients who had received an adequate amount of treatment for early syphilis, neurosyphilis occurred in only 7.5 per cent of those whose treatment had been continuous but in 22.6 per cent of the group of patients who had received treatment irregularly.

Wile and his co-workers¹⁹² show that as for neurosyphilis in general the absence or inadequacy of treatment of early syphilis is a predominant factor in the precocious development of dementia paralytica and tabes dorsalis.

188 Matras, A. Zur Frage des positiven Liquors im 1. Jahre der Syphilis, *Arch f. Dermat. u. Syph.* **175** 85 (Jan. 2) 1937.

189 Moore, M., and Merritt, H. H. Dementia Paralytica at the Boston Psychopathic Hospital, *New England J. Med.* **215** 108 (July 16) 1936, Rôle of Syphilis of Nervous System in Production of Mental Disease. Survey of Various Forms of Neurosyphilis Occurring at Boston Psychopathic Hospital from 1912 to 1934, *J. A. M. A.* **107** 1292 (Oct. 17) 1936.

190 Peers, J. H. The Occurrence of Tumors of the Central Nervous System in Routine Autopsies, *Am. J. Path.* **12** 911 (Nov.) 1936.

191 O'Leary, P. A., and others. Cooperative Clinical Study in the Treatment of Syphilis. Asymptomatic Neurosyphilis, *Arch. Dermat. & Syph.* **35** 387 (March) 1937.

192 Wile, U. J., Poth, D. O., and Barney, B. F. Dementia Paralytica and Tabes. A Study with Reference to Precocious Development, *J. A. M. A.* **105** 1329 (Oct. 26) 1935.

As the result of an anthropometric investigation of 27 patients with dementia paralytica, Guirdham¹⁹³ concludes that no single body type exists in this group

Nonne¹⁹⁴ considers the genesis of neurosyphilis at some length and expresses the opinion that treatment of early syphilis has little or nothing to do with the prevention or encouragement of the subsequent development of neurosyphilis except hasten its onset. The entire matter, he says, is to be summed up in Ricord's statement "Each individual has his own [kind of] syphilis"

As an argument for the existence of a neurotropic strain of *S. pallida*, Jormann¹⁹⁵ presents the instance of marital partners in both of whom tabes dorsalis developed

Merritt, Putnam and Campbell¹⁹⁶ compared the histologic picture of the brains of patients who had died of dementia paralytica with anatomic changes which by experimental maneuvers they were able to produce in the cerebral cortical substance of dogs. From this experience they suggest that the degenerative changes in the cortex in dementia paralytica may be regarded as secondary to anoxemia produced by endarteritis of small cortical vessels

Syphilitic Epilepsy—Bruetsch and Bahr¹⁹⁷ clearly differentiate between convulsions occurring in patients with neurosyphilis and true idiopathic epilepsy. The term syphilitic epilepsy is used only for neurosyphilis associated with convulsive seizures which resemble idiopathic epilepsy in all respects and which leave no signs of organic disease of the brain. Clinically, differentiation from true idiopathic epilepsy is difficult and sometimes impossible. The condition is rare, but cases have been reported by reliable observers. To this small group the present authors add a full clinical and pathologic description of 5 cases

General Clinical Considerations—Winkelman¹⁹⁸ brings to completion his exhaustive monographic discussion of syphilitic diseases of the

193 Guirdham, A. The Body Type of the General Paralytic, *J. Neurol. & Psychopath.* **16** 363 (April) 1936

194 Nonne, M. Erinnerungen und Bekenntnisse auf dem Gebiet der Neurologies, *Deutsche Ztschr. f. Chir.* **248** 177 (Dec.) 1936

195 Jormann, A. Conjugale Tabes mit ähnlichen klinischen Symptomen, *Schweiz. med. Wchnschr.* **67** 226 (March 13) 1937

196 Merritt, H. H., Putnam, R. J., and Campbell, A. C. P. Pathogenesis of Cortical Atrophy Observed in Dementia Paralytica, *Arch. Neurol. & Psychiat.* **37** 85 (Jan.) 1937

197 Bruetsch, W. L., and Bahr, M. A. Syphilitic Epilepsy, *Am. J. Syph., Gonorr. & Ven. Dis.* **21** 255 (May) 1937

198 Winkelman, N. W. Syphilis of the Spinal Cord, *Am. J. Syph., Gonorr. & Ven. Dis.* **20** 421 (July) 1936

spinal cord Langworthy and his co-workers¹⁹⁹ assemble the results of their earlier contributions, previously reviewed,^{1b} regarding the effect of the lesions of tabes dorsalis on the control of micturition Rubritius²⁰⁰ presents the results of similar studies, with similar conclusions Muschet²⁰¹ particularly emphasizes the value of repeated cystometric examination of patients with disturbance of the neurologic control of micturition to determine whether progress, arrest or improvement is taking place

Bujadoux and Gourevitch²⁰² have devised a rather complicated apparatus for detecting the presence of ataxia of the pupil to a measured light stimulus before the development of a true Argyll Robertson phenomenon The method, they say, is of great value in the early diagnosis of neurosyphilis

In a discussion of the medical and surgical aspects of Charcot joints Epstein²⁰³ brings out that the condition is primarily an orthopedic problem Antisyphilitic treatment is valueless so far as the arthropathy is concerned

THE TREATMENT OF NEUROSYPHILIS

The Choice of Method—Wagner-Jauregg²⁰⁴ reviews the general considerations involved in the treatment of patients with neurosyphilis In his opinion the most important of these is to realize that neurosyphilis develops early in the course of syphilitic infection and should be detected by early routine examination of the cerebrospinal fluid A positive reaction at this stage does not necessitate the immediate induction of fever, the simple methods should be tried first On the other hand, fever therapy is urgently indicated if the patient comes under observation with clinical neurosyphilis

The discussion regarding the superiority of inoculation malaria over fever induced by artificial means or vice versa seems for the moment to have abated In a preliminary report of a proposed long-term study,

199 Langworthy, O R, Dees, J E, and Lewis, L G Abnormalities of Micturition Due to Syphilis of the Nervous System, *Am J Syph, Gonorr & Ven Dis* **20** 364 (July) 1936

200 Rubritius, H Die Miktionsstörungen der Tabiker, *Wien klin Wchnschr* **50** 311 (March 5) 1937

201 Muschet, M Cystometric Studies The Value of Follow-Up Examinations, *Am J M Sc* **192** 693 (Nov) 1936

202 Bujadoux, A, and Gourevitch, F Les troubles du pre-Argyll-Robertson, *Presse med* **45** 550 (April 10) 1937

203 Epstein, S H Medical and Surgical Aspects of Charcot Joints, *Am J Syph, Gonorr & Ven Dis* **20** 386 (July) 1936

204 Wagner-Jauregg, J Die Behandlung der luetischen Erkrankungen des Nervensystems, *Therap d Gegenw* **77** 385 (Sept) 1936

however, Barnacle and his co-workers²⁰⁵ observed no significant difference in the clinical outcome for patients treated by one means or the other. Both groups had received tryparsamide.

For patients in whom treatment with fever is indicated the question which has been most recently raised concerns the desirability or the best method of adding tryparsamide to the scheme of treatment.

The Combination of Fever Therapy with Tryparsamide—Maletz and Solomon²⁰⁶ present the results of their study of 87 patients with dementia paralytica who had been treated with malaria followed by tryparsamide. They were able to show better results for this group than for patients treated with malaria alone. Like Wile and Hand²⁰⁷ they discovered no correlation between the clinical course and the serologic findings in the cerebrospinal fluid.

Hinsie and Blalock²⁰⁸ observed a group of 146 patients for from six months to four years after the administration of ten paroxysms of artificially induced fever, which totaled about seventy hours. These patients fell into three groups: (1) those who had fever only, (2) those who received tryparsamide after the course of fever treatment and (3) a smaller number who received tryparsamide just before each fever treatment. These authors conclude that while benefit is derived from treatment with fever alone, the best results follow the use of tryparsamide subsequent to fever therapy. They especially bring out, however, that there seems to be no advantage to the administration of a dose of tryparsamide just before each fever treatment.

The Results of Fever Treatment of Neurosyphilis—Wile and Hand²⁰⁷ are much encouraged by the average course of events in their group of 474 patients treated with malaria. One hundred and eighty-two of these patients came under observation with dementia paralytica, the remainder had various other forms of neurosyphilis. In patients with juvenile dementia paralytica little benefit was observed, but more than half the adults showed improvement. This was especially true for those who had had a relatively acute onset of symptoms and who did not have obvious deterioration. Half the patients with tabes and 95 per cent of those with asymptomatic neurosyphilis achieved a satisfactory

205 Barnacle, C. H., Ebaugh, F. G., and Ewalt, J. R. Treatment of Dementia Paralytica. Comparative Study of Combined Artificial Hyperpyrexia and Tryparsamide Versus Therapeutic Malaria, a Preliminary Report, *J. A. M. A.* **107** 1031 (Sept. 26) 1936.

206 Maletz, L., and Solomon, H. C. Spinal Fluid Reaction in General Paresis as Modified by a Combination of Therapeutic Malaria and Tryparsamide, *Am. J. Syph., Gonorr. & Ven. Dis.* **21** 287 (May) 1937.

207 Wile, U. J., and Hand, E. A. Ten Years' Experience with Malaria in Neurosyphilis, *Am. J. Syph., Gonorr. & Ven. Dis.* **20** 630 (Nov.) 1936.

208 Hinsie, L. E., and Blalock, J. R. Treatment of General Paralysis by Ultra High-Frequency Heating, *New York State J. Med.* **36** 1951 (Dec. 15) 1936.

result. The authors particularly emphasize in this group the lack of correlation between the clinical course and the changes in the reactions to serologic tests of the cerebrospinal fluid.

Paulian²⁰⁹ succeeded in producing malaria in 1,165 (86 per cent) of a group of 1,359 patients with dementia paralytica. The remainder were immune to inoculation. Seventy-four per cent of those in whom malaria ran a typical course showed either "cure" or marked improvement for varying periods of observation.

Nichole and his co-workers²¹⁰ and Wheelock²¹¹ report smaller series of patients, with essentially similar results. In a review of the literature Neymann²¹² found reports on 853 patients with parenchymatous neurosyphilis to whom treatment with electropyrrexia had been given. Of the 754 patients with dementia paralytica, 213 (28 per cent) were accredited with complete remission, and 260 (35 per cent) were reported as being improved. Twenty, or 2.5 per cent, had died as a result of treatment. Only 9 patients with juvenile dementia paralytica treated with electropyrrexia have been reported on. Of these, 2 were markedly improved, 5 were improved and 2 were unimproved. Ninety patients with tabes are reported on, 54 being improved and 36 unimproved.

Bennett²¹³ points out that neither chemotherapy nor inoculation malaria relieves the lightning pains or gastric crises of tabes dorsalis of more than half the patients so treated. In contrast, by a combination of simultaneous chemotherapy and artificially induced fever he was able to relieve symptoms in all of his 11 patients.

The Determination of the Prognosis of Inoculation Malaria—Paulian²¹⁴ advances the interesting suggestion that the determination of the permeability of the blood-brain and the blood-cerebrospinal fluid barriers to arsenic before and after malaria therapy may be a valuable

209 Paulian, D. La malariothérapie dans le traitement des syphilis nerveuses, *Ann d mal ven* **31** 561 (Aug) 1936.

210 Nichole, J. E., Harrison, G. J., Nichol, W. D., and Hutton, E. L. A Follow-Up Study of General Paralysis, with Special Reference to Malarial Therapy, *Proc Roy Soc Med* **30** 623 (March) 1937.

211 Wheelock, M. C. The Treatment of Paresis Based on an Analysis of One Hundred and Thirteen Patients, *J Iowa M Soc* **27** 107 (March) 1937.

212 Neymann, C. A. The Effect of Artificial Fever on the Clinical Manifestations of Syphilis and the Treponema Pallidum, *Am J Psychiat* **93** 517 (Nov) 1936.

213 Bennett, A. E. Fever Therapy in Tabes Dorsalis. Relief of Gastric Crises and Lightning Pains by the Use of the Kettering Hypertherm, *J A M A* **107** 845 (Sept 12) 1936.

214 Paulian, D. La perméabilité des meninges à l'arsenic dans la paralysie générale avant et après la malariothérapie, *Ann de med* **39** 375 (April) 1936, Ueber den feinen Wirkungsmechanismus der Malaria-therapie in den Veränderungen hamato-meningealer Schranken, *Wien med Wchnschr* **87** 264 (March 6) 1937.

prognostic sign. Normally, he says, arsenic may be detected in the cerebrospinal fluid only in traces, if at all, after the intravenous injection of a trivalent arsenical. For 12 patients with dementia paralytica, however, the arsenic content of the cerebrospinal fluid was repeatedly determined by the method of Martin and Pien (which he fully describes) from four to ten hours after the intravenous injection of 0.45 Gm of neoarsphenamine. Before the induction of malaria the average arsenic content of the cerebrospinal fluid was 0.001 Gm per hundred cubic centimeters, afterward the value had fallen to 0.0002 Gm per hundred cubic centimeters. In general, also, the lowest values after inoculation malaria were obtained for the patients who showed the greatest clinical improvement. Paulian feels therefore that, in addition to the great theoretical interest, the determination may be of some practical importance.

Artificially Induced Fever, General Considerations—Krusen²¹⁵ presents a summary of current knowledge concerning fever therapy produced by physical means. The discussion of the physiology of artificially induced fever is especially complete. Stecher and Solomon²¹⁶ add a detailed study of the complications of artificially induced fever based on 1,000 consecutive treatments. Nausea with vomiting was the most common complication which they observed, circulatory collapse, the most serious.

Wilbur and Stevens²¹⁷ report the morbid anatomic observations for 2 patients who died after treatment in an electric lamp cabinet and, in comparison, those for a third patient who died of sunstroke. They conclude:

The most consistent findings in these three cases were congestion, petechial hemorrhages and diffuse early hepatic necrosis. Evidence of damage to the central nervous system was found in only one case. This was characterized by degenerative changes in the astrocytes.

Blood Versus Mosquito for Transmission of Malaria—Boyd and his collaborators²¹⁸ have been engaged in the development of a method for easily maintaining facilities for the transmission of therapeutic malaria by mosquitoes. The observations of Kusch and others²¹⁹ show

215 Krusen, F. R. The Present Status of Fever Therapy Produced by Physical Means, *J. A. M. A.* **107** 1215 (Oct 10) 1936.

216 Stecher, R. M., and Solomon, W. M. The Complications and Hazards of Fever Therapy. Analysis of One Thousand Consecutive Fever Treatments with the Kettering Hypertherm, *Ann. Int. Med.* **10** 1014 (Jan) 1937.

217 Wilbur, E. L., and Stevens, J. B. Morbid Anatomic Changes Following Artificial Fever, with Report of Autopsies, *South. M. J.* **30** 286 (March) 1937.

218 Boyd, M. F., Stratmen-Thomas, W. K., and Kitchen, S. F. Modifications in a Technique for the Employment of Naturally Induced Malaria in the Therapy of Paresis, *Am. J. Trop. Med.* **16** 323 (May) 1936.

219 Kusch, E., Milam, D. F., and Stratmen-Thomas, W. K. General Paresis Treated by Mosquito-Inoculated Vivax (Tertian) Malaria, *Am. J. Psychiat.* **93** 619 (Nov) 1936.

that the efforts are worth while. In their comparative study of 72 patients treated by mosquito inoculation and 363 patients treated by blood inoculation, these authors discovered that the main differences in the clinical course was that in the former patients it was milder, thereby permitting a longer period of infection. The differences in results were striking. Twenty-six per cent of the patients given mosquito inoculation gained a sustained remission, and 49 per cent were improved, for those given blood inoculation the results were 19 and 36 per cent, respectively.

Boyd and Kitchen²²⁰ show that *Plasmodium falciparum* may be kept in mosquito culture and is readily transmissible to man. In contrast to the situation with *Plasmodium vivax*, the Negro possesses no racial immunity to *P. falciparum*. A small clinical experience indicates that the organism has great powers of invasiveness and, therefore, that it must be used with caution. Clinical results, however, are promising.

Blackwater Fever—Foy and Kondi²²¹ inoculated 106 patients who had various psychoses with blood from some one of a group of 58 patients with blackwater fever. In none of the patients who were inoculated did hemoglobinuria develop.

Fever Therapy as an Office Procedure—Davison, Lowance and Barnett²²² advocate the employment of fever therapy as an office procedure. McClure²²³ on the other hand, adopts a much more defensible position.

Fever therapy is not simple and to be safely given demands special training. At the present time there are appearing advertisements of fever-producing machines for office use. Nothing is so apt to discredit fever therapy as this indiscriminate use under the belief that it is an innocuous thing.

Special Methods of Fever Therapy—Kulchar and Anderson²²⁴ recommend the use of divided doses of typhoid H antigen for the pro-

220 Boyd, M. F., and Kitchen, S. F. A Further Note on the Infectiousness of Anopheline Mosquitoes Infected with *P. Vivax* and *P. Falciparum*, *Am J Trop Med* **17** 245 (March) 1937, Observations on Induced *Falciparum* Malaria, *ibid* **17** 213 (March) 1937.

221 Foy, H., and Kondi, A. Researches on Blackwater Fever in Greece. IV. Experimental Investigations into the Existence of Haemolytic Strains of Malaria and/or Other Specific Parasites in Blackwater Fever, *Ann Trop Med* **30** 423 (Dec.) 1936.

222 Davison, H. M., Lowance, M. I., and Barnett, C. F. Hyperpyrexia. An Evaluation of Its Use in Office Practice, *M Rec* **143** 253 (March 18) 1936.

223 McClure, R. D. Artificial Fever Therapy, *South M J* **29** 704 (July) 1936.

224 Kulchar, C. V., and Anderson, L. E. Divided Doses of Typhoid H Antigen Vaccine in the Treatment of Neurosyphilis, *Am J Syph, Gonorr & Ven Dis* **21** 413 (July) 1937.

duction of fever in the treatment of neurosyphilis, especially of the aged or the infirm Ogata ²²⁵ suggests inoculation with the virus of typhus as a ready means of producing fever! Werner ²²⁶ employed a less typhus severe rickettsia infection (five day fever) for the same purpose

Acetarsone—Pakenham-Walsh and Rennie ²²⁷ report encouraging results from the preliminary study of the oral administration of acetarsone to patients with dementia paralytica They feel that the drug should have an extensive trial

The Treatment of Atrophy of the Optic Nerve—Since 1916 Schacherl ²²⁸ has treated 114 patients with primary atrophy of the optic nerve by the subdural method Sixty-nine of the patients were observed for more than three years In 53 of this group (77 per cent) the author believes that treatment was successful

An interesting theoretical discussion of the genesis of atrophy of the optic nerve is presented by Lauber ²²⁹ This author seeks to explain the underlying phenomena as due to an interaction between a fall in systemic blood pressure and a rise in intra-ocular tension, thereby causing mechanical impeding of the circulation to the retina and optic nerve

Folk, ²³⁰ working on a similar theory, combines paracentesis bulbi with the subcutaneous injection of atropine in the treatment of various conditions of the retina and optic nerve Some benefit was obtained by 6 patients with primary atrophy of the optic nerve whom he treated by this method

SYPHILIS AND PREGNANCY

The fact that untreated syphilis in the mother is capable of exerting a deleterious effect on the outcome of pregnancy is now well established and needs no further documentation The frequency of this effect and the conditions other than treatment of the disease in the mother which

225 Ogata, N Ueber Rickettsiatherapie der Neurosyphilis, Wien klin Wchnschr **49** 1225 (Oct 2) 1936

226 Werner, H Neuere Ergebnisse aus dem Gebiete der Tropenhygiene V Zur Methodik der Arzneimittelpfung bei Malaria und zur Fieberbehandlung der Paralyse (Rickettsienimpfung), Deutsche med Wchnschr **62** 903 (May 29) 1936

227 Pakenham-Walsh, R, and Rennie, A T Oral Administration of Stovarsol in Cases of Neurosyphilis Certified as Insane, Lancet **1** 982 (April 24) 1937

228 Schacherl, M Zwanzig Jahre endolumbaler Salvarsanbehandlung der Atrophia nervi optici tabetica, Wien klin Wchnschr **50** 313 (March 5) 1937

229 Lauber, H Treatment of Atrophy of the Optic Nerve, Arch Ophth **16** 555 (Oct) 1936

230 Folk, M L Paracentesis and Atropine in the Treatment of Optic and Retinal Atrophies Preliminary Report, Am J Ophth **20** 511 (May) 1937

modify it are, however, still in need of clarification. Paley's²³¹ communication is therefore timely. In a study of 617 pregnancies of women with syphilis this author discovered that 173 (28 per cent) eventuated unfavorably as a direct result of the maternal infection.

The effect of the duration of syphilis in the mother on the outcome of pregnancy is strikingly shown. Disregarding other factors, the outcome of the pregnancy was unfavorable in 51 per cent of the instances in which the mother had had syphilis for less than two years, in only 25 per cent of the instances in which the infection was of more than two but less than five years' duration and in only 19 per cent of the instances in which the infection had been present five years or more.

The author demonstrates equally clearly that in this group the end-result of the pregnancy is related to the amount of antisyphilitic treatment which the mother receives during pregnancy. Unfavorable end-results due to syphilis occurred in 46 per cent of the cases in which the mother received less than 4 injections of an arsenical plus heavy metal, but in only 27 per cent of the cases in which from 4 to 7 injections were given and in only 14 per cent of the cases in which 8 or more injections were given. The influence of the trimester in which treatment was begun was less striking and seemed to be related only to the total amount of treatment administered.

The Influence of Pregnancy on Syphilis—There has long been the clinical impression that pregnancy exerts a beneficial effect on the course of syphilitic infection. Kemp²³² sought to examine the question experimentally. Four groups each of 12 rabbits were employed, all were infected with syphilis by a standard method. A group of females was repeatedly bred after infection until each animal had had three litters. A group of females and a group of males were treated with filtered urine of pregnant women for fifteen weeks, and the fourth group, half of them males and half of them females, were carried as controls. The results suggested to Kemp that while pregnancy exerts an appreciable inhibiting effect on the course of syphilitic infection, it is not the only factor responsible for the altered course of the disease in the female.

CONGENITAL SYPHILIS

The Genesis of Congenital Syphilis—Levaditi and his group²³³ theorize concerning the mode of infection of the child with congenital

231 Paley, S. S. Syphilis in Pregnancy, New York State J. Med. **37** 585 (March 15) 1937.

232 Kemp, J. E. The Effect of Pregnancy and of Female Sex Hormones in Modifying the Course of Syphilis in Experimental Animals, J. Infect. Dis. **60** 32 (Jan.-Feb.) 1937.

233 Levaditi, C., Goldman, M., and Rousset-Chabaud. Mécanisme de la transmission héréditaire de l'infection syphilitique, Compt. rend. Soc. de biol. **120** 854, 1935.

syphilis, particularly with regard to the manner by which the non-syphilitic children of a syphilitic mother escape infection. After considering the various possibilities they conclude that the spirochete must be filtered out of the maternal circulation by the placenta. Local factors in that organ then determine whether or not fetal infection occurs. Kemp and Rosahn²³⁴ reached somewhat similar conclusions from their unsuccessful attempts to produce congenital syphilis in the rabbit. They concluded that either the placenta filters out the spirochete or the fetus destroys it, the evidence favors the former hypothesis.

General Considerations—Hoffmann,²³⁵ Maddox²³⁶ and many others present general summaries of the problems of congenital syphilis which do not lend themselves well to review. Cregor and Dalton²³⁷ plead for the development of methods for the earlier accurate diagnosis of syphilis in the new-born.

Clinical Phenomena in Congenital Syphilis—Josephs²³⁸ observes that anemia is present in a large percentage of children with congenital syphilis. Further, he says that congenital syphilis is one of the commonest causes of severe anemia during the first three months after the neonatal period.

Glickman and Minsky²³⁹ call attention to the occurrence of enlargement of one sternoclavicular articulation in patients with late congenital syphilis. Jung²⁴⁰ discusses the various skeletal manifestations of congenital syphilis which he observed in roentgenograms of 6 stillborn syphilitic fetuses and 56 syphilitic infants under 1 year of age.

"Bismuth Lines" in the Bones of Infants—Caffey²⁴¹ studied roentgenograms of the bones of children under treatment with bismuth and of those whose mothers had received bismuth during pregnancy. He

234 Kemp, J. E., and Rosahn, P. D. Experimental Study of Congenital Syphilis, Including a Study of the Infectiousness of Blood, Uterus and Placenta of Pregnant Rabbits with Early Syphilis, *Bull. Johns Hopkins Hosp.* **60**: 45 (Jan) 1937.

235 Hoffmann, E. Congenital Syphilis in the Light of Thirty Years' Investigation of the Spirochete and Twenty-Five Years' Experience with Salvarsan, *J. Pediat.* **9**: 569 (Nov.) 1936.

236 Maddox, R. C. Congenital Syphilis, *Arch. Pediat.* **53**: 692 (Oct.) 1936.

237 Cregor, F. W., and Dalton, J. E. Syphilotoxemia in the New-Born, *Arch. Dermat. & Syph.* **35**: 580 (April) 1937.

238 Josephs, H. W. Anaemia of Infancy and Early Childhood, *Medicine* **15**: 307 (Sept.) 1936.

239 Glickman, L. G., and Minsky, A. A. Enlargement of One Sternoclavicular Articulation. A Sign of Congenital Syphilis, *Radiology* **28**: 85 (Jan) 1937.

240 Jung, T. S. Congenital Bone Syphilis. Roentgenologic Diagnosis in Infants Under One Year of Age, *Chinese M. J.* **50**: 352 (April) 1936.

241 Caffey, J. Changes in the Growing Skeleton After the Administration of Bismuth, *Am. J. Dis. Child.* **53**: 56 (Jan) 1937.

found a definite relation both between the time (in the stage of the development of the fetus or child) that the bismuth was administered and the position of the "bismuth line" in the long bones and between the amount of bismuth which had been given and the width of the "metallic" shadow in the roentgenogram. Experimental studies of growing puppies, however, seemed to indicate that the roentgen-opaque shadow laid down at the epiphysial line after the administration of bismuth was largely a calcified cartilaginous matrix, with a relatively low content of bismuth.

The Eye in Congenital Syphilis—A first examination of the statistics which Berens, Kerby and McKay²⁴² present seems to suggest that syphilis is the cause of only 5.3 per cent of blindness in children. These authors bring out, however, that "hereditary and congenital" blindness, which accounts for more than half the blindness among children in the schools for the blind, must include some blindness due to syphilis, so that the actual incidence of syphilitic blindness is higher than appears.

From a group of 247 children with congenital syphilis Lennarson and Jeans²⁴³ selected 143 for special study of the condition of the eyes. Sixty-six per cent of this specially studied group (38 per cent of the entire group) were found to have some syphilitic lesion of the eye. Forty-three per cent of all the children over 2 years of age manifested interstitial keratitis. The maximum frequency of this condition occurred at the age of 8 (57 per cent). Chorioretinitis was found in only 1 infant but in 13 per cent of the older children whose fundi were examined. Atrophy of the optic nerve was about half as frequent.

For one third of the 1,010 patients with late congenital syphilis studied by the Cooperative Clinical Group, Cole,²⁴⁴ acting as spokesman, says that interstitial keratitis was the principal initial diagnosis.

Juvenile Dementia Paralytica—A careful study of the pathologic changes in the brains of 7 children with juvenile dementia paralytica is reported by Haas²⁴⁵. He observed that the changes, in general, were those characteristic of dementia paralytica in adults, but with certain additions. The changes in the children's brains were more striking, there was greater evidence of degeneration and lesions were present in the cerebellum in all 7 cases.

242 Berens, C., Kerby, C. E., and McKay, E. C. The Causes of Blindness in Children. Their Relation to Preventive Ophthalmology, *J. A. M. A.* **105** 1949 (Dec. 14) 1935.

243 Lennarson, V. E., and Jeans, P. C. Congenital Syphilis of the Eyes. A Clinical Study, *Am. J. Syph., Gonorr. & Ven. Dis.* **21** 90 (Jan.) 1937.

244 Cole, H. N., and others. Late Prenatal Syphilis, *Arch. Dermat. & Syph.* **35** 564 (April) 1937.

245 Haas, H. T. A. Beitrag zur Pathologie und Pathogenese der juvenilen Paralyse, *Ztschr. f. d. ges. Neurol. u. Psychiat.* **156** 405 (Oct. 16) 1936.

The picture of juvenile dementia paralytica which Grotjahn²⁴⁶ presents is not a happy one, but it is in keeping with the experience of others. This author treated with malaria 57 children who had dementia paralytica. The average age at the onset of symptoms was 14 years for the 25 who had had no previous treatment, 13 years for the 22 who had had treatment in childhood and 9.3 years for the 10 who had been treated in infancy. In none of these children, however, had treatment been adequate. None gained a complete remission after malaria treatment, 4 could not be traced and, of the remainder, 18 had a partial remission and 35 were unimproved or dead.

The Treatment of Congenital Syphilis—For the treatment of congenital syphilis Givan and Villa²⁴⁷ recommend the use of acetarsone intravenously. They have given 43 children a total of 1,010 injections of this drug in weekly doses of from 0.2 to 1 Gm., and they say that it is useful, safe and well tolerated.

Gerth²⁴⁸ sounds a note of caution regarding the use of acetarsone. He observed death attributable to the drug in a child 3½ months of age, and he knows of other instances. He feels therefore that if the drug is to be used, it should be given in small doses.

THIRD GENERATION SYPHILIS

Wendel²⁴⁹ presents a case of third generation syphilis which fulfils all the Fournier-Finger criteria. The case of Rein and Shostac²⁵⁰ is also convincing and fails to fulfil the formal criteria only because in the second generation lesions of syphilis did not develop shortly after birth.

BEJEL

Bejel has been brought to light entirely through the contributions of Hudson,²⁵¹ who observed it during his service as chief of the clinic in

246 Grotjahn, M. Zur Klinik und Psychologie der juvenilen Paralyse, Monatschr. f. Psychiat. u. Neurol. **92** 299 (Feb.) 1936, **93** 19 (March) 1936.

247 Givan, T. B., and Villa, G. The Intravenous Use of Acetarsone in Congenital Syphilis, J. Chemotherapy **13** 97 (Oct.) 1936.

248 Gerth, R. Zur Frage der Heilung der kongenitalen Lues des Säuglings mit kleinen Spirociddosen, Monatschr. f. Kinderh. **67** 46 (Sept. 19) 1936.

249 Wendel, F. Ein Beitrag zur Frage der Uebertragung der kongenitalen Syphilis auf die nächste Generation, Med. Klin. **32** 976 (July 17) 1936.

250 Rein, C. R., and Shostac, F. Probable Case of Third Generation Syphilis. Report of a Case, Arch. Dermat. & Syph. **34** 877 (Nov.) 1936.

251 Hudson, E. H. Hyperkeratoses and Depigmentations in Bejel, Ann. Trop. Med. **30** 3 (April) 1936, Bejel. Nonvenereal Syphilis, Arch. Dermat. & Syph. **33** 994 (June) 1936. Hudson, E. H., and Crosley, S. S. The Influence of Bejel on the Second Generation, Brit. J. Dermat. **48** 288 (June) 1936. Hudson, E. H. Mucocutaneous Syphilis (Bejel) in Syria, New England J. Med. **215** 392 (Aug. 27) 1936, Bejel—The Childhood Syphilis of the Bedouins. Oral Manifestations, J. Am. Dent. A. **24** 219 (Feb.) 1937, Kahn and Kolmer-Wassermann Reactions in Bejel, Am. J. Syph., Gonorr. & Ven. Dis. **21** 45 (Jan.) 1937.

Den-*ez-Zoi*, Syia Bejel, he says, is an Arabian name for the non-venereal syphilis usually acquired during childhood by the seminomad Bedouin villagers of the middle division of the Euphrates valley. It is extremely prevalent (he estimates that 90 per cent of the adults either have or have had the disease) and participates in many of the clinical characteristics of yaws. It occurs, however, far north of the usual geographic locations in which yaws is seen, and there are certain differences in the clinical manifestations of the two diseases.

YAWS

Not much of the considerable literature on yaws is proper material for this review. A few contributions, however, which bear on the relation between yaws and syphilis are of interest. Turner²⁵² presents the results of an extensive series of inoculation experiments on 79 patients with yaws and 10 with syphilis and concludes:

In man, yaws confers an immunity to reinfection. Resistance to auto-inoculation becomes manifest early in the course of the disease and obtains in most persons during the period in which active lesions are present. Immunity to reinoculation of heterologous strains of yaws spirochetes develops slowly during the course of the natural disease. Within the first years, reinoculation may give rise to a modified or an abortive attack of yaws but after a period of 10 years, the majority of yaws-infected persons are refractory to reinoculation. Interruption of the normal course of the disease by treatment seems to retard the development of immunity.

Syphilis also confers an immunity to yaws which is as great as, if not greater than, that conferred by yaws itself.

In the experimental rabbit the same author²⁵³ discovered that organisms from patients with yaws and from patients with syphilis produced characteristic and different disease processes and that each retained its identity during many passages through animals.

Weller²⁵⁴ has been conducting a painstaking histopathologic study of the viscera of patients with "Haitian treponematoses" which were submitted to him from the Haitian General Hospital at Port au Prince. At the conclusion of the more recent article^{254b} he says:

In view of the impossibility of establishing an indubitable clinical diagnosis for each patient, this study must not be considered as offering certain proof of either the unity or the duality of yaws and syphilis. It is intended only as an objective presentation of factual material. However, one of three conditions must exist: either yaws and syphilis are essentially the same disease, or the group of patients

252 Turner, T. B. The Resistance of Yaws and Syphilis Patients to Reinoculation with Yaws Spirochetes, *Am J Hyg* **23** 431 (May) 1936.

253 Turner, T. B. Studies on the Relationship Between Yaws and Syphilis, *Am J Hyg* **25** 477 (May) 1937.

254 Weller, C. V. (a) The Pathology of the Aorta in Haitian Treponematoses, *Am J Syph, Gonorr & Ven Dis* **20** 467 (Sept) 1936, (b) The Visceral Pathology in Haitian Treponematoses, *ibid* **21** 357 (July) 1937.

here considered has an extremely high incidence of syphilis and the evidences of this disease alone are apparent in the viscera, or yaws and syphilis, if different diseases, produce identical visceral lesions

RESISTANT SYPHILIS

Drug Resistance—Netherton²⁵⁵ reports 2 instances of conjugal syphilis of the early type in each of which only the wife showed resistance to drugs. In 1 case the infection was resistant to the arsenicals and to bismuth and mercury, while in the other case resistance was manifested to three of the most commonly used arsenicals. This resistance to both arsenic and the heavy metals, says the author, tends to invalidate the theory of a strain of *S. pallida* which is resistant to arsphenamine.

The patient whom Hood²⁵⁶ reports on maintained lesions in the mouth which showed *S. pallida* on dark field illumination for almost two years. During the first year intensive treatment with arsphenamine and mercury was given, after which there was a lapse in treatment. When the patient returned the lesions healed promptly when treated with an experimental arsenic preparation, and no recurrences were observed. Treatment was continued with arsphenamine, and sixteen years later the patient was found to be clinically well. There was, however, still a positive reaction to serologic tests for syphilis.

Schoch²⁵⁷ reports an unusual experience. He inoculated rabbits with spirochetes from a patient with treatment-resistant syphilis and was able to retain the resistance of the strain during passages through animals.

Seroresistance—O'Leary²⁵⁸ points out that the manifestation of a persistently positive reaction to serologic tests for syphilis during treatment has many possible interpretations. The correct one may be obtained by the interpretation of the history, physical examination and serologic tests of blood and cerebrospinal fluid by a shrewd clinician.

INTERRELATION OF SYPHILIS AND TUBERCULOSIS AND OTHER FEATURES

Pulmonary Tuberculosis—Leader²⁵⁹ brings up the problems which the diagnosis and treatment of pulmonary tuberculosis may present

255 Netherton, E. W. Arsphenamine-Resistant Syphilis, *Arch. Dermat. & Syph.* **35** 607 (April) 1937.

256 Hood, B. J. An Unusual Case of Arsphenamine Resistance, *Am. J. Syph., Gonorr. & Ven. Dis.* **21** 97 (Jan.) 1937.

257 Schoch, M. A. Fortdauer der Therapieresistenz eines Pallidstammes im Tierversuch, *Klin. Wchnschr.* **16** 306 (Feb. 27) 1937.

258 O'Leary, P. A. Wassermann Fastness, *Journal-Lancet* **56** 464 (Sept.) 1936.

259 Leader, S. A. Pulmonary Tuberculosis and General Paresis, *Am. Rev. Tuberc.* **34** 776 (Dec.) 1936.

when it occurs in patients hospitalized because of mental disease. In patients with dementia paralytica, because of their generally poor condition, tuberculosis is particularly likely to develop and this of course precludes fever therapy. The patient must be treated for the tuberculosis, if for no other reason than to prevent the spread of the disease to others, and the author recommends that tryparsamide be used for the treatment of the neurosyphilis.

Old Age—In discussing the treatment of elderly persons with syphilis Netherton²⁶⁰ brings out the necessity of individualization. For patients with active syphilis in any stage treatment must be given with sufficient vigor to control progression, heal lesions and prevent infectiousness. For elderly persons with late quiescent syphilis, however, treatment may be gentle or may be omitted.

Race—Hazen²⁶¹ estimates that syphilis is at least twice as prevalent among Negroes as in the white race and points out the terrific cost which it levies. There are certain racial differences in the clinical course of the disease, but the response to treatment is the same.

Vonderlehr and his collaborators²⁶² compared the morbidity rates for three groups of Negro men: 399 with syphilis who had never received treatment, 201 who were presumably normal and 275 with syphilis who had received treatment during the first two years of the infection. They say:

The results indicate that the cardiovascular system is the most commonly involved in the late syphilitic process and the aorta is the most commonly involved structure in so-called latent syphilis in the adult male Negro.

Morbidity in the male Negro with untreated syphilis far exceeds that in a comparable presumably nonsyphilitic group.

Adequate antisyphilitic treatment prevented all forms of clinical relapse during the first fifteen years of the infection, whereas only one fourth of the Negroes with untreated syphilis were normal.

Cardiovascular and central nervous system involvement were from two to three times as common in the untreated syphilis group as in a comparable group receiving even inadequate treatment.

GENERAL CONSIDERATIONS

Almkvist²⁶³ is dissatisfied with the time-honored division of syphilis into three stages and proposes a new classification, which he bases on

²⁶⁰ Netherton, E. W. The Management of Syphilis in Elderly Persons, *Cleveland Clin Quart* **3** 205 (July) 1936.

²⁶¹ Hazen, H. H. Syphilis in the American Negro, *Am J Syph, Gonorr & Ven Dis* **20** 530 (Sept) 1936.

²⁶² Vonderlehr, R. A., Clark, T., Wenger, O. C., and Heller, J. R., Jr. Untreated Syphilis in the Male Negro. A Comparative Study of Treated and Untreated Cases, *J A M A* **107** 856 (Sept 12) 1936.

²⁶³ Almkvist, J. Die Ergebnisse meiner histologischen Untersuchungen über syphilitische Veränderungen, *Wien med Wchnsch* **86** 1266 (Nov 14) 1936, *The Pathology of Syphilis in a New Light*, *Brit J Dermat* **49** 1 (Jan) 1937.

the histopathologic pictures of the different lesions. The classification is rather complicated and does not seem destined to gain general use.

Stokes,^{42b} in the Prose White oration, sums up the practical problems in the control of syphilis and the methods which are at hand for solving them.

Chesney²⁶⁴ discusses the needs for research on the control of syphilis before the Conference on Venereal Disease Control. After a step by step summary of the needs in all the various phases of the problem, he concludes:

The real answer to the whole question is, of course, quite simple. There are only two needs, as is always the case in matters of research. The first of these is to find men and women with imagination and ideas, and then interest them in the problem, the second is to secure for these individuals the means which will permit them to work out their ideas unhampered. If these two needs can be fulfilled, then all that is necessary is to let nature take its course. One does not need to worry about the result.

264 Chesney, A. M. Research Needs in the Control of Syphilis, *Am J Syph, Gonorr & Ven Dis* **21** 121 (March) 1937.

CORRECTION

In a recent article entitled "Influence of Copper and a Liver Fraction on Retention of Iron" (*ARCH INT MED* **60** 474 [Sept] 1937), Barer and Fowler erroneously used the term liver rather than liver extract in referring to the results obtained by Cheney and Niemand (footnote 11) and by Powers and Murphy (footnote 12). In 1931 Powers and Murphy stated, "Liver extract is of no value in the treatment of these types of chronic secondary anemia" (*The Treatment of Secondary Anemia, J A M A* **96** 504 [Feb 14] 1931). Murphy, however, in a subsequent article stated that in secondary anemia "treatment by means of intramuscular injections of solution of liver extract (Lederle) together with adequate doses of iron by mouth is the most effective" (*Treatment of Secondary Anemia, with Special Reference to the Use of Liver Extract Intramuscularly, ARCH INT MED* **51** 656 [May] 1933).

Book Reviews

Eugenical Sterilization A Reorientation of the Problem By Abraham Myerson, J G Ayer, T J Putnam, C E Keeler and Leo Alexander, the Committee of the American Neurological Association for the Investigation of Eugenical Sterilization Price, \$3 Pp 211 New York The Macmillan Company, 1936

This book constitutes the report of the special committee which was appointed in 1934 by the American Neurological Association to survey the problem of eugenical sterilization. It is a clear, straightforward and readable discussion of the problem of heredity in relation to neurology and psychiatry and of the feasibility of attempting to control diseases with a hereditary tendency by a program of sterilization, either compulsory or voluntary. The writer of each section has reviewed both the older and the more recent literature thoroughly and discusses his problem in the light of the best modern medical and genetic thought.

The medical literature dealing with heredity and sterilization has hitherto presented an almost insurmountable obstacle to any one interested in this subject. Thoughtful perusal indicates that it can truthfully be said that this book is a valuable contribution to medical and genetic literature, not only because of its authoritative and penetrating analysis of the problems considered but because of the many erroneous theories and hypotheses, until recently firmly embedded in medical thought, which it so conclusively proves to be valueless, without foundation and even absurd.

It is impossible to give in a short space all the subjects that are considered in detail. Some of the more important conclusions, however, are too valuable to omit. An adequate history of eugenics and sterilization is given, and a chapter is devoted to the pertinent laws now in force in the various states of the United States and in foreign countries.

In considering the main arguments for sterilization some interesting points are brought out in the present work. It is demonstrated that mental disease is actually not increasing and that it is only the recognition and commitment of psychiatric patients to institutions that is increasing in locations where better facilities for diagnosis and treatment of these conditions have developed. The authors conclude that "there is nothing to indicate that mental disease and mental defectives are increasing, and from this standpoint there is no evidence of a biological deterioration of the race. What is certain is that the hospital population is increasing." The authors believe that too much stress has been laid on the expense of caring for the mentally sick.

The chapter dealing with points of view regarding sterilization contains the opinions of many persons regarding sterilization, both pro and con. It is impossible to give these opinions in their entirety, but it is evidently the author's intention that the reader should recognize that the statements issued by exponents of a sweeping program of compulsory sterilization are misleading and, to say the least, "overdogmatic and socially excessive." The majority of recent opinions quoted are in favor of a properly regulated program of voluntary sterilization limited to persons afflicted with disorders which have been definitely shown to be transmissible.

There is an excellent and well condensed chapter on genetics and its relation to eugenics. The most prominent geneticists of the present time have expressed the opinion that the race can be benefited by good breeding and by the elimination of undesirable stocks, but they are not convinced that man knows enough about mental diseases and the effects of the social structure to manipulate in a successful way the procreation of the race.

There is an excellent chapter on the inheritance of mental diseases which represents a cautious attempt to review the situation as it exists today. The

authors reach the important conclusion that there is little real information on which to base any farflung theory of the heredity of psychoses or feeble-mindedness.

They believe that no definite evidence exists which warrants the postulate of any widespread unitary trait back of the psychoses, feeble-mindedness, epilepsy and the like.

The most recent studies on the inheritance of manic depressive psychosis, dementia praecox, feeble-mindedness and epilepsy are considered in detail but cannot be quoted here. When modern methods are employed, the only definite statement that can be made in regard to the inheritance of dementia praecox, manic depressive psychosis, epilepsy and feeble-mindedness is that these conditions occur in certain families in a higher incidence than in the general population but that inheritance in a mendelian ratio cannot be demonstrated.

There is a short chapter on chronic progressive neurologic diseases known to have some tendency toward hereditary transmission. This chapter does not deal with all the neurologic conditions known to have a hereditary tendency but rather gives a brief summary of some of the literature concerning the diseases in which hereditary transmission is most marked. A chapter is also devoted to a discussion of the possible effect of a sterilization program on crime. It is pointed out that there is almost no evidence to show that criminality, as such, could be affected by sterilization.

There is a short chapter on genius and eugenics, wherein it is pointed out that had a program of sterilization been carried out several centuries ago, much talent would have been lost to the world, a formidable list of the names of great men with insane relatives is given in proof of this.

The concluding chapter consists of the recommendations of the committee. These, unfortunately, cannot be given in detail. It is agreed that voluntary sterilization alone should be considered in the few conditions in which a hereditary tendency exists. The committee does not believe that sterilization of normal persons can have any place in preventing the production of diseased individuals except in a few rare instances. It is recommended that one or several boards consisting of persons who have had special training and experience in the problems involved carry out sterilization procedures and that adequate legal protection be given them.

The diseases for which selective voluntary sterilization of affected persons is recommended by the committee are as follows: (1) Huntington's chorea, hereditary atrophy of the optic nerve, familial Friedreich's ataxia and certain other disabling diseases recognized to be hereditary, (2) feeble-mindedness of the familial type, (3) dementia praecox, (4) manic-depressive psychosis, and (5) epilepsy, when known to be hereditary. It is stated, however, that in most of these diseases sterilization can have but little effect on the occurrence of the conditions in generations to come. The committee recommends that further research be carried out on large sections of the population to determine the "psychiatric constitution" of the community. It is recommended that a permanent committee be appointed to organize research in these directions.

The committee stresses the important fact that in a large measure no great or radical change in the complexion of society can result from a sterilization program such as the one recommended. The committee concludes that "there is no social or biological emergency which need hurry us into a widespread sterilization program based on fear and propaganda."

Each chapter in the book is well summarized in a paragraph or two at the end, and this will enable the lay reader to grasp the conclusions without going through the statistical material from which the conclusions were drawn. A complete bibliography is appended.

The Adrenals By Arthur Grollman Price, \$5.00 Pp 410 Baltimore Williams & Wilkins Company, 1936

Few authors today would have the courage to attempt a book on the adrenal glands, as the subject is in a constant state of flux and in spots is highly contro-

versal New observations are being made with startling rapidity, and time must elapse to enable them to be verified and evaluated. The author surmounts these difficulties by dismissing or ignoring much with which he does not agree. After one has read the book there is left a decided impression that the work contains a little too much of what Grollman thinks about the adrenal glands and not enough of what others have thought and are still thinking about them. In other words, unless one is fully acquainted with this phase of endocrinology too much confidence should not be placed in many of his statements or interpretations of facts. For example, Grollman dismisses the fact that by the administration of a properly balanced mixture of electrolytes, adrenalectomized animals can be kept alive indefinitely with adrenal cortex extract, by attributing other workers' success along this line to incomplete adrenalectomy or to the presence of adrenal rests. To be sure, considerable skill is required in keeping such animals alive, but it can be done and has been done by men whose ability to perform complete adrenalectomy or to discover adrenal rests cannot be questioned. (Allers, W. D., and Kendall, E. C. *The Influence of Diet and Mineral Metabolism on Dogs After Suprarenalectomy*, Proc. Staff Meet., Mayo Clin. **10** 406-409 [June 26] 1935, Am. J. Physiol., to be published; Harrop, G. A., Soffer, L. J., Nicholson, W. A., and Strauss, Margaret. *Studies on the Suprarenal Cortex. IV. The Effect of Sodium Salts in Sustaining the Suprarenalectomized Dog*, J. Exper. Med. **61** 839-860 [June 1] 1935.) Unfortunately, at the time the book was written the discoveries concerning the important relationship of potassium in the diet to the disturbance in physiology which accompanies adrenal insufficiency had not been published. Had the book been written later, a statement such as the following might not have been made on pages 193 and 194:

"The claim that administration of salts or Ringer's solution admixed with the food or in lieu of the animal's supply of drinking water, permits the indefinite survival of adrenalectomized rats has not been confirmed by the author nor by other observers. The apparent indefinite survival and normal growth of animals on a replacement therapy consisting solely of inorganic salts must be attributed to incomplete adrenalectomy."

The foregoing remarks exemplify only one of a number of such faults. Equally disparaging comments can be made about the author's interpretation of the part played by the kidneys in adrenal insufficiency, methods of preparation and standardization of the adrenal cortex hormone and so forth.

In spite of a number of such shortcomings the book has considerable merit. It covers the territory fairly completely, and the references given are representative and about as complete as one could expect. In addition to a detailed account of most of the work done on the adrenal cortex, there are chapters on the gross and the microscopic anatomy of the adrenal glands, the chemistry, physiology and pharmacology of epinephrine and the relationship of the adrenal glands to other endocrine organs, toxins, infections, immunity and surgical shock. Much of this material cannot be found in any other one printed work on the subject, and on this account alone the book will be of considerable use to any one interested in this phase of medicine. The section devoted to clinical considerations is fairly complete, but it is suggested that any one who wishes to treat diseases of the adrenal glands would do better to consult the original works, references to which are given. In this connection it is only fair to state that Grollman makes no claims to extensive clinical experience in the treatment of diseases of the adrenal glands. Considerable space is devoted to the author's opinions concerning the cause of the symptoms which occur in the adrenogenital syndrome. It will be recalled that this syndrome is found chiefly in cases of adrenocortical tumor of women and is characterized largely by hirsutism, amenorrhea, hypertension and other symptoms very similar, if not identical, to those that occur in pituitary basophilism, as described by Harvey Cushing. Grollman attributes these symptoms to the proliferation and persistent activity of the so-called border, or "x," zone of the adrenal cortex, which in human beings normally disappears in the first year of life. For this particular zone of tissue Grollman has introduced the term "androgenic tissue." As a hypothesis, his interpretation is at least as satisfactory, if not more so, than any hypothesis which has been advanced to explain the

curious changes which occur in this disease. Furthermore, his hypothesis suggests a new line of approach to the studies of these tumors, and it is to be hoped that further histopathologic studies and experimental work will be forthcoming shortly along these lines.

Tissue Immunity By Reuben L. Kahn, M.S., D.Sc. Price, \$7.50 Pp 726, with 54 charts, 107 tables, 7 illustrations, 2 plates in color. Springfield, Ill., Charles C. Thomas, Publisher, 1936.

The author feels that the response of fixed tissues to antigenic stimuli has not received the attention it deserves in comparison with the amount of study that has been devoted to phagocytes and circulating antibodies. He has therefore injected antigens into various tissues—most commonly the skin—of rabbits and observed the inflammatory response, the anchoring and destruction of antigen, the local necrosis and sometimes the effect on circulating antibody. Horse serum was the antigen usually employed. The immunity of tissues to bacterial or other toxins received no detailed study.

In the experimental demonstration of the importance of tissues in the response to antigens, the technologic approach is varied in many ways, and numerous features of the response are topics of discussion in the first sixteen chapters of the book. It is obviously impracticable even to list these topics here. Each chapter contains a summary and, excepting the first, a section dealing with clinical considerations. The two final chapters are devoted to "theoretical and practical aspects of tissue immunity." The numerous tables and graphs are of exceptionally consistent intelligibility.

The clinician, the pathologist, the bacteriologist, the teacher and student of immunology, the specialists in dermatology, pediatrics and allergy, and the biologist, to all of whom this book has been recommended, should be warned that the experimental work has been confined exclusively to rabbits and that the results and interpretations have been transmuted into clinical considerations on evidence that is not altogether convincing.

The quantitative aspect of these studies is emphasized, yet in many instances there is a tenfold (1,000 per cent) difference between successive amounts in the titrations recorded, in the measurement of precipitin the notoriously inferior antigen dilution method is exclusively employed. Furthermore horse serum is a mixture of antigens, and accurate quantification of the corresponding mixture of antibodies is difficult. In many kinds of experiments the results of simple direct tests certainly cannot be interpreted with confidence.

It is to be hoped that one of the "new views" given clinical consideration on page 262 will not mislead the clinician into a potentially dangerous experiment. "The fact that large quantities of antigen can be injected intravenously in immunized animals without indications of shock is of interest in connection with practical therapeutics. It may be that the same patients who respond with local inflammation to an injection of antitoxin into a tissue [positive cutaneous reaction?], due to previous immunization with horse serum, may show no untoward effect to the injection of the antitoxin intravenously. The size of the dose is evidently important. It is the small dose that is likely to produce shock while the large dose, at least in rabbits, is less likely to produce shock."

The accounts of the experiments often are repetitious. The book could easily be condensed to a considerable extent without sacrifice of clarity or content.

Medical Classics, Volume 1, Number 1 Compiled by Emerson C. Kelley, M.D. Price, \$10 per year Pp 78, with 9 illustrations. Baltimore. Williams & Wilkins Company, 1936.

This is a new venture, it is not a journal in the ordinary sense, though it is to be published periodically, and, on the other hand, scarcely a book, though this first number in permanent binding would materially embellish the shelves of any library.

As stated in its preface, "Medical Classics" aims to awaken the interest of all medical workers in the historical side of their profession. This first number deals

with Sir James Paget, that shrewd Victorian, who said, "To be brief is to be wise, to be epigrammatic is to be clever," and who eventually became one of the leading surgeons of his time

There is a reproduction of the Millais portrait which gives a sufficiently good idea of Paget's appearance at the height of his career. A short biographic sketch traces his development from 1834, when, at the age of 20 and a student at St Bartholomew's Hospital, he described *Trichina spiralis*, until his death in 1899. Then follow his bibliography and a little paragraph called "Eponyms," which gives references to his articles originally describing Paget's abscess, Paget's disease of the bone, Paget's disease of the nipple, Paget's tumor and Paget's mixture of mercury and potassium iodide.

Best of all, however, is the reprinting of what most authorities regard as Paget's three medical classics, entitled "On a Form of Chronic Inflammation of Bones (Osteitis Deformans)," "Additional Cases of Osteitis Deformans" and "On Disease of the Mammary Areola Preceding Cancer of the Mammary Gland." Each of these reprints is accompanied with a reproduction of the first page of the original article that is revived, and the first reprint includes also a reproduction of the illustrations which accompanied the paper.

"Medical Classics" aims to be useful and not merely ornamental. No student can read volume 1, number 1, without feeling a sense of gratitude at being so pleasantly introduced to a great doctor who wrote perfect medical English. All teachers interested in the historical method of education will be equally pleased with the new publication, because "Medical Classics" gives promise of opening many doors that too often are securely barred. In future numbers it is planned to reproduce other medical classics that in their original form are to be found in comparatively few libraries that are easily accessible to hungry-minded beginners. Certainly the compiler of "Medical Classics" is to be warmly congratulated, may his efforts be crowned with all the success they deserve!

The Lung By William Snow Miller, M.D., Sc.D. Emeritus Professor of Anatomy, University of Wisconsin. Price, \$7.50. Pp 209, with 152 illustrations. Springfield, Ill. Charles C. Thomas, Publisher, 1937.

In a day of prolific publication, when so many books and articles show evidence of immaturity and seem to be largely activated by a desire to "get into print," it is a bit startling and very comforting to encounter a book that is the result of almost half a century of study and deliberation. Even if Dr. Miller had never before published even a single article, this book would make him the foremost authority of the day on the anatomy of the lung.

The book is divided into twelve chapters, in which are gathered together the results of the author's investigations on the lung, its blood vessels, its lymphatic system and its nerves. A chapter is devoted to the pleura and another chapter to a historical sketch of the development of anatomic knowledge from the time of Vesalius to the present. In all controversial situations the author states his position and defends it.

The book is profusely illustrated with cuts of excellent quality. These include photographs, photomicrographs, reconstructions and schematic drawings. Many are in color.

The book is uniformly excellent, and it is difficult to single out any portion of it for special mention. The section on the lymphatic system of the lung, pleura and bronchus gives evidence of the painstaking way in which the work was carried out, although the same attention to detail is shown in all sections.

The book is especially recommended for a place in the reference library, where it should prove extremely valuable, both for its contents and for its bibliography.

In the preface the author expresses his gratitude to a group of friends who made this publication possible. Attention should be directed also to another group of friends and a host of admirers who will affectionately treasure this book, apart from its scientific worth, simply because it was written by Dr. Miller. One of the characteristics of a truly great man is his ability to retain the love and affection of his friends and students, regardless of the eminence he attains.

**Verhandlungen der deutschen Gesellschaft für Kreislaufforschung IX
Tagung** Edited by E B Koch, M D, Bad Nauheim Paper Price, 15
marks Pp 378, with numerous illustrations, tables and graphs Dresden
Theodor Steinkopff, 1936

This volume reports the proceedings of the 1936 meeting of the *Deutsche Gesellschaft für Kreislaufforschung*, which last April was held at Bad Nauheim. The meeting lasted for three days, and the program included thirty-eight papers.

The meeting began with a presidential address. Then there followed a series of papers which, if delivered as they are printed, must have varied considerably in length, and finally many of these papers were discussed in a competent and interesting manner.

Naturally, as one might judge from the name of the society, the program centered around vascular disease, and it is interesting to realize from what a variety of angles such a general topic was discussed. There was a good deal of statistical data presented which dealt with the increasing importance of vascular disease in Germany. Then there were papers dealing with vascular insults caused by various poisons, by trauma or by electricity. Evidently in Germany, just as in this country, there is at the moment considerable interest in peripheral vascular disease, for this subject received a good deal of attention. There were also papers dealing with other baffling problems, like the relationship of occupation to arterial degeneration and the surgical treatment of hypertension. Finally, there was a group of papers dealing with cardiovascular physiology, and new methods were presented for studying and recording pulse waves and heart sounds.

The volume, as a whole, contains a good many excellent papers, which no doubt are available in other periodicals. One of the chief interests of the book lies in the fact that it covers, more or less in summary form, a wide range of subjects and gives one a chance to perceive at a glance how many of the aspects of cardiovascular disease are today being studied in several different German clinics.

The Physiology and Pharmacology of the Pituitary Body By H B Van Dyke, M D, Professor of Pharmacology, Peiping Union Medical College. Price, \$4.50 Pp 594, with 55 illustrations. Chicago University of Chicago Press, 1936.

The author states that he has written this volume in an attempt to give an adequately documented account of the experimental work on the pituitary body during the past fifteen years, and in this he has included such clinical work as has appeared to contribute to the knowledge of this subject. The book is clearly written, well printed and well illustrated.

The difficulty of the task which the author set for himself is well marked off by his statement that in accomplishing it more than five thousand reports were consulted. Incidentally, about three thousand of these are cited in the bibliography which appears at the end of the volume.

Any book might deserve praise which was written in a conscientious effort to clear up the present chaotic state of knowledge regarding the pituitary gland and which gave a fair and critical analysis of the literature dealing with hormones and antihormones of this peculiar body. This book deserves particularly high commendation not only because it has been put together in a scholarly fashion but because it is a good deal more than an accurate and sincere bibliographic compilation. The conflicts in opinion of various observers are clearly set forth and made to coincide as far as possible, so that one feels a sense of progress in knowledge. The writing is good, so that the book is alive and interesting. Inevitably it will prove of great usefulness to all students, investigators and clinicians who have any interest in modern endocrinology.

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SUSCEPTIBILITY OF MAMMALIAN ERYTHROCYTES TO HEMOLYSIS WITH HYPOTONIC SOLUTIONS

A FUNCTION OF DIFFERENCES BETWEEN DISCOIDAL VOLUME
AND VOLUME OF A SPHERE OF EQUAL SURFACE

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Clinicians as well as physiologists have displayed interest in the varied susceptibilities to hemolysis by hypotonic solutions of the erythrocytes of different species of mammals and of human erythrocytes under different pathologic conditions. The variations have been somewhat vaguely ascribed to differences in "osmotic resistance" and in "permeability" (due, in turn, to constitutional anomalies and to differences in the age of the erythrocytes). The possibility that differences in the dimensions of erythrocytes might be responsible for differences in susceptibility to hypotonic hemolysis has, however, been mentioned from time to time, and certain correlations in this respect have been pointed out.

Chauffard¹ said he considered that the wide "resistance span" in hemolytic jaundice was an expression of heterogeneity of cell population in respect to diameter. Valléry-Radot and Lhéritier² noted that the resistance to hemolysis of the erythrocytes of different species of mammals varied directly with the diameter of the cells. Ponder³ in

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1 Chauffard, M. A. *Pathogenie de l'ictère congénital de l'adulte*, *Semaine med* **27** 25, 1907.

2 Valléry-Radot, P., and Lhéritier, A. *Parallelisme entre la résistance globulaire aux solutions chlorurées sodiques et la dimension de l'hématie chez les mammifères*, *Compt rend Soc de biol* **82** 195, 1919.

3 Ponder, E. *The Measurement of Red Cell Volume*. VI *The Different "Fragility" of the Red Cells of Various Mammals*, *J Physiol* **83** 352 (Feb 9) 1935.

a recent paper has presented a correlation between the resistance to hemolysis and the volume of the erythrocyte after conversion to a spherical form. None of these observations, however, has more than suggested that the dimensions of the erythrocyte are in some way closely related to the problem, for none has satisfactorily depicted a mechanism at work under the experimental conditions of the "resistance" test.

In 1922 Gansslen⁴ suggested a dynamic explanation of the characteristically increased susceptibility of the erythrocytes of chronic familial hemolytic jaundice to destruction by hypotonic solution of sodium chloride. His statement may be translated as follows:

The fact that in the microcytes of hemolytic jaundice one is dealing with altered, namely, approximately spherical, erythrocytes, averaging larger than normal in volume, allows one to explain the decreased resistance in the following manner: The active forces in resistance experiments are osmotic forces. The sphere is the form which has the greatest volume with the least surface, it contains the greatest amount of paraplasma in the smallest envelope. Therefore, in order to reach osmotic equilibrium, the erythrocytes of hemolytic jaundice will take up more water than normal erythrocytes. Because of their form, however, they will be less capable of accommodating it. Their effort to take up more water results in a disproportion to the size of the envelope, which in resistance experiments finds its expression in an early destruction or rupture of the cell, so that hemolysis begins in much higher concentration than normal.

Gansslen presented no experimental data supporting his hypothesis except a few measurements confirming the increased cell volume relative to the diameter in hemolytic jaundice, which had already been observed by Naegeli and Alder.⁵ Von Boros⁶ referred to Gansslen's work but stated that similarly shaped erythrocytes without altered resistance to hemolysis are found in the blood of patients with anemia due to hemolysis. Both he and Meulengracht⁷ regarded the spherocytosis and decreased resistance in hemolytic jaundice as unrelated phenomena resulting from rapid production of blood. Chauffard¹ and Naegeli⁸ considered the decreased diameter and resistance as unrelated and due to a fundamental constitutional defect in the formation of erythrocytes.

4 Gansslen, M. Ueber hamolytischen Ikterus, *Deutsches Arch f klin Med* **140** 210, 1922.

5 Alder, cited by Naegeli.⁸

6 von Boros, J. Ueber Grosse, Volumen und Form der menschlichen Erythrozyten und deren Zusammenhang. II. Die Mikrozytose beim hamolytischen Ikterus, *Wien Arch f inn Med* **12** 255, 1926.

7 Meulengracht, E. Der chronische hereditäre hamolytische Ikterus, Leipzig, Werner Klinkhardt, 1922.

8 Naegeli, O. Blutkrankheiten und Blutdiagnostik, ed 3, Berlin, Walter de Gruyter & Co., 1919, p 408.

Fortunately, Haden's⁹ recent work has again emphasized the differences in the form (thickness-diameter ratio) of erythrocytes of different susceptibility to hemolysis by hypotonic solution. His conclusions are in accord with Gansslen's hypothesis, which has been extended to an explanation of the differences in susceptibility to hemolysis of the erythrocytes of certain other blood dyscrasias, notably hypochromic anemia. Jacobs¹⁰ has pointed out that considerable differences exist in the increase in volume necessary to produce hemolysis of various types of erythrocytes. He has assumed that because of its biconcave shape the erythrocyte may swell considerably in hypotonic solutions without a significant increase in its original surface. If this is so, it is possible that differences in shape may be entirely responsible for differences in susceptibility to hemolysis and in apparent permeability.

Nevertheless, if differences in the shape of erythrocytes are to explain entirely differences in susceptibility to hemolysis by hypotonic solutions, significant differences in strictly osmotic behavior must be shown not to exist. That is to say, the percentage increase in the original volume of erythrocytes of different susceptibilities to hemolysis must be the same when equilibrium is established with a given hypotonic solution. Moreover, for the support of Gansslen's hypothesis it is essential to show that differences in shape can quantitatively explain differences in susceptibility to hemolysis. And, finally, further support would be given to the geometric hypothesis if differences in shape, rather than in permeability, could be shown to account for differences in the time necessary for a given hypotonic solution to produce hemolysis of different types of erythrocytes.

EXPERIMENTS

Percentage of Increase in Erythrocyte Volume in Hypotonic Plasma—Our approach to the problem was to examine the osmotic behavior of erythrocytes of different susceptibilities to hypotonic hemolysis.¹¹ Determinations were made of the percentage increase in volume of samples of erythrocytes after suspension in progressive dilutions of homologous oxalated plasma. In all, forty-five observations were made on the erythrocytes of normal human beings, dogs, rabbits, pigs and sheep and on the erythrocytes of patients with severe hypochromic anemia and of patients with chronic familial hemolytic jaundice. In each instance a suitable amount of venous blood was rendered incoagulable by the addition of 0.05 cc. of a 20 per cent solution of potassium oxalate to each 5 cc. of blood. The volume of

9 Haden, R. L. (a) The Mechanism of the Increased Fragility of the Erythrocytes in Congenital Hemolytic Jaundice, *Am J M Sc* **188** 441, 1934, (b) *Tr A Am Physicians* **49** 308, 1934.

10 Jacobs, M. H. The Permeability of the Erythrocyte, *Ergebn d Biol* **7** 1, 1931.

11 Castle, W. B., in discussion on Haden,^{9b} p. 326.

the erythrocytes of each sample was then determined by means of the Wintrobe¹² hematocrit tubes. On the basis of this value, homologous ovalated plasma was added to an uncentrifugated portion of the original blood in amounts sufficient to yield a sample with a cell volume of 30 per cent. In a series of nine test tubes 1 cc of the 30 per cent suspension of erythrocytes was added to such amounts of homologous plasma and distilled water that the original volumes of erythrocytes were suspended in equal amounts of concentrations of homologous plasma of 1, 0.95, 0.9, 0.85, 0.8, 0.75, 0.7, 0.65 and 0.6, respectively. A sample of the erythrocyte suspension in each tube was pipetted into each of two Wintrobe hematocrit tubes. All the hematocrit tubes from one experiment were then placed in the centrifuge at the same time and rotated at 2,500 revolutions per minute for thirty minutes.

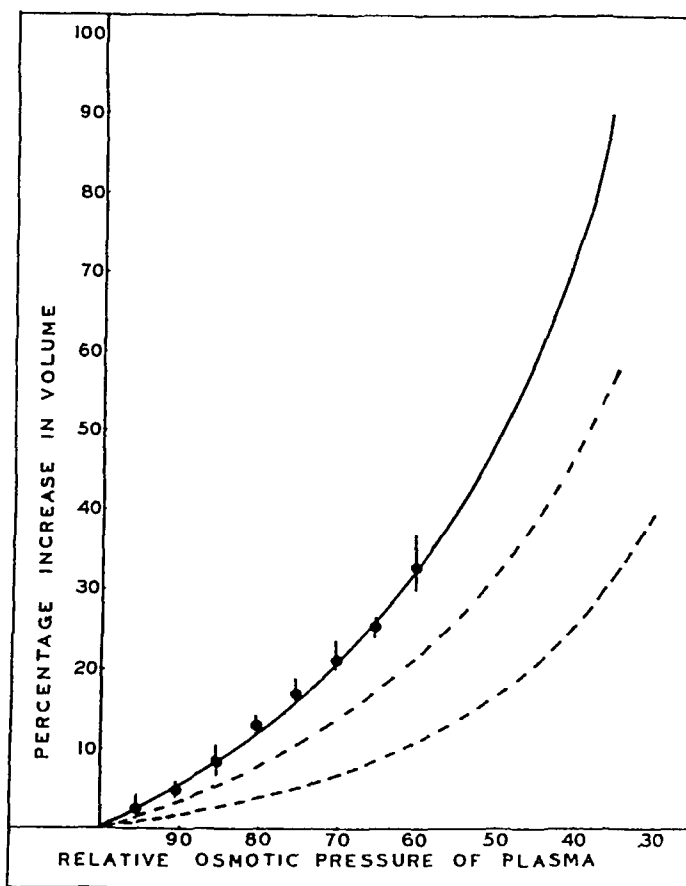


Chart 1—Average values obtained from forty-five experiments on the percentage increase in equilibrium volume of seven types of erythrocytes in hypotonic ovalated plasma (solid circles). The vertical line through the solid circle shows the extremes of average values obtained for any type of erythrocyte (table 2). The upper curve (solid line) gives the best approximation of the average values and is based on the formula $V_e = \left[\frac{1(100-b)}{P_e} + b \right] - 100$, the value 51 being used for b . The middle curve is constructed from this formula, the value 69.4 being used for b . The lowest curve is described by a value of 82.9 for b . An explanation of the theoretical significance of these curves is given in the text.

¹² Wintrobe, M. M. The Direct Calculation of the Volume and Hemoglobin Content of the Erythrocyte, *Am J Clin Path* 1: 147, 1931.

After centrifugation the volume of erythrocytes was measured in all the hematocrit tubes showing no trace of hemolysis. In table 1 are presented illustrative data obtained from an experiment on the erythrocytes of a dog.

From the averages of the uncorrected duplicate hematocrit determinations were computed the respective percentage increases in the equilibrium volume of the erythrocytes in each plasma concentration over the volume in undiluted plasma in the first tube. In table 2 are shown the average results of all the observations for each species and pathologic condition. The final averages of these values are also shown in table 2 and are plotted as solid circles in chart 1. The vertical lines in chart 1 indicate the extremes of the average data for any type of erythrocyte. The data in table 2 apparently indicate that the observed differences in the per-

TABLE 1—Data from Experiment (9/18/35) on Equilibrium Volumes of Dog Erythrocytes

Concentration or relative osmotic pressure of plasma	1.00	0.95	0.90	0.85	0.80	0.75	0.70	0.65	0.60
Volume percentage of erythrocytes	13.33	13.13	14.01	14.65	14.98	15.67	16.10	16.66	17.29
Duplicates	13.29	13.57	14.02	14.01	15.08	15.59	15.92	17.53	17.35
Average percentage	13.31	13.35	14.01	14.33	15.03	15.63	16.01	17.12	17.32
Absolute increase in equilibrium volume	0.00	0.04	0.70	1.02	1.72	2.32	2.70	3.81	4.01
Percentage increase in equilibrium volume	0.00	0.30	5.30	7.70	12.90	17.40	20.30	28.60	30.10

TABLE 2—Average Percentage Increase in Equilibrium Volumes of Various Types of Erythrocytes

Type of Erythrocyte	No of Experiments	Concentration or Relative Osmotic Pressure of Plasma*								
		1	0.95	0.9	0.85	0.8	0.75	0.7	0.65	0.6
Hypochromic anemia	8	0		5.8		14.3		22.8		37.1
Normal human being	8	0		4.7		12.9		21.5		33.2
Dog	5	0	1.8	4.0	6.6	12.2	15.9	20.4	26.5	30.6
Hemolytic jaundice	5	0	2.6	4.6	10.7	12.9	15.9	20.1	24.3	29.8
Rabbit	5	0	2.9	4.2	9.9	13.6	17.4	23.9	H	H
Pig	8	0	0.8	4.9	7.7	12.1	18.9		H	H
Sheep	6	0	4.1	5.2	7.8	12.9	16.9	22.3	H	H
Averages		0	2.4	4.8	8.5	12.9	17.0	21.8	25.4	32.6

* H indicates that some hemolysis was present in these concentrations after centrifugation.

centage increase in volume for all the various types of erythrocytes were within the experimental error of the method. Thus the osmotic behavior of the various types of erythrocytes appears to be uniform.

Microscopic Observations of Alteration in Form of Erythrocytes in Hypotonic Plasma—The problem was, therefore, to account for the wide differences in susceptibility to hypotonic hemolysis of erythrocytes undergoing apparently similar percentage increases in volume in hypotonic plasma. Gansslen's⁴ hypothesis implies that because of the biconcave or invaginated form of the erythrocyte in isotonic solution, swelling is possible without an increase in surface until a spherical form is reached. Attainment of the spherical form will therefore result in destruction of the cell, since thereafter an increase in surface must accompany any further increase in volume. However, it is essential for this hypothesis to assume that the erythrocyte in swelling behaves like a balloon with a liquid interior rather than like a sponge which swells

without changing its form. On this point agreement is not complete, although the critical observations of Ponder and Millar¹³ demonstrated a decrease in the diameter of the cell as swelling occurred, and Haden⁹ has recently found an increase in the thickness-diameter ratio of erythrocytes in dried films of blood prepared from progressive dilutions of heparinized blood with distilled water. Nevertheless, it seemed desirable to observe under the microscope the changes in form of erythrocytes of different susceptibilities to hypotonic hemolysis when suspended in various dilutions of oxalated plasma, especially when two types of erythrocytes were suspended together in the same hypotonic plasma.

A drop of a dilute suspension of any type of erythrocyte in homologous oxalated plasma was placed on a flat slide and covered with a thin cover glass. Immediately after being sealed with paraffin the preparation was examined under an oil immersion lens with the stage of the microscope in a *vertical* position and illuminated by a strong source of artificial light. In this way a view of different aspects of the corpuscles is obtained as they rotate or oscillate in sinking through the plasma. All types of corpuscles showed the biconcave discoidal or, rarely, the "cup" form in isotonic oxalated plasma. If, however, a suspension of any type of corpuscle was examined in hypotonic oxalated plasma of such concentration that over half the cells were hemolyzed, many of the remaining intact cells were seen to be almost spherical, but some were still somewhat biconcave. If serial observations were made in increasingly dilute samples of plasma, the proportion of almost or entirely spherical cells increased.

That a given concentration of hypotonic plasma had a greater effect on the original form (not volume) of erythrocytes of relatively diminished resistance to osmotic hemolysis than on the form of erythrocytes possessing a greater resistance to hemolysis was best demonstrated by study of a preparation containing two such different types of erythrocytes, for example, a mixture of sheep and human cells. When suspended in suitable human plasma of 0.5 concentration, many of the sheep cells were hemolyzed, but those remaining intact were readily identifiable because of their small size when compared with the human corpuscles. Many of the sheep corpuscles were noted to be almost spherical, sometimes exhibiting only a slight depression or "pip" at one point, whereas the human erythrocytes exhibited a decidedly biconcave form. If, however, human corpuscles were observed in plasma of 0.34 concentration, many of them, like those of the sheep when suspended in plasma of 0.5 concentration, were noted to have become almost spherical.

These observations make it clear that the approach to the spherical form is associated with destruction of each type of corpuscle. Moreover, a concentration of hypotonic plasma producing a large proportion of nearly spherical forms of a given type of erythrocyte produces fewer nearly spherical forms of any type of corpuscle with greater resistance to hypotonic hemolysis.

Calculation of Susceptibility to Hypotonic Hemolysis on the Basis of the Form of the Erythrocyte—The qualitative behavior of the erythrocytes just described suggests that the swelling of erythrocytes, as implied by Gansslen's⁴ hypothesis and by Jacobs,¹⁰ is not accompanied with an increase in surface until a spherical form is attained. If this is so, the resistance to hemolysis of a given type of erythrocyte might be expressed by the percentage of difference between the original discoidal volume of the erythrocyte in isotonic solution and the volume of a sphere

13 Ponder, E., and Millar, W. G. Alterations in the Form of Mammalian Erythrocytes in Hypotonic Plasma, *Quart. J. Exper. Physiol.* **15** 1, 1925. Millar, W. G. The Diffraction Method of Measuring the Diameter of Erythrocytes, *Proc. Roy. Soc., London*, s B **99** 264, 1926.

with a surface equal to that of the erythrocyte in isotonic solution ^{14a} In subjecting this supposition to quantitative test, difficulty is at once encountered because of the impossibility of making accurate measurements of the erythrocyte under the experimental conditions This obstacle has been fully discussed by Ponder ^{14b} Nevertheless, it seemed worth while to attempt to estimate the geometric characteristics of the various samples of erythrocytes which had been studied with regard to equilibrium volumes

From those observations the uncorrected volume percentage of erythrocytes in each sample of oxalated venous blood was already known A count of the number of erythrocytes per cubic millimeter in each sample was made, and by means of the formula $\frac{\text{cell volume percentage}}{\text{millions of cells per cubic millimeter}} \times 10 = \text{mean corpuscular volume (cubic microns)}$, the uncorrected mean corpuscular volume (V_o) was calculated Films from each sample of oxalated venous blood were immediately prepared and stained with Wright's stain From these preparations the mean cell diameter (D_o) was determined by measuring 500 erythrocytes by the method of Price-Jones ¹⁵ The mean corpuscular thickness (T_o) was then calculated by means of the formula $T_o = \frac{4V_o}{\pi D_o^2}$, on the assumption of von Boros ¹⁶ that the erythrocyte is a right cylinder of known volume and diameter The volume, diameter and thickness of this cylinder being known, its surface was found, and finally the volume (V_s) of a sphere with this surface The percentage of increase in volume necessary to cause the discoidal erythrocyte to assume a spherical form without change in surface would then be represented by the formula $\frac{V_s - V_o}{V_o}$ The essential average data for each type of erythrocyte are shown in table 3

The observations on the percentage increase in equilibrium volumes of the erythrocytes were made in diluted homologous oxalated plasma in order to avoid the preliminary washing and centrifugating which would have been involved if hypotonic solution of sodium chloride had been employed Since it was impracticable to obtain sufficient oxalated plasma for determining the range of susceptibility to hemolysis of the erythrocytes of each sample, this information was secured by using appropriate dilutions of solution of sodium chloride according to the method of Worthley and one of us (G A D) ¹⁷ A mean value was taken as lying halfway between the concentrations for "definite" and "partial" In quantitative studies of hemolysis this value was shown to correspond fairly well to the steepest part of the S-shaped summation curve obtained, or to about 50 per cent hemolysis Other observations showed that the range of susceptibility to hemolysis of normal human and sheep erythrocytes in serial dilutions of oxalated plasma cor-

14 Since this manuscript was submitted for publication similar conclusions have been published by Ponder as follows Ponder, E (a) The Spherical Form of the Mammalian Erythrocyte III Changes in Surface Area in Disks and Spheres, *J Exper Biol* **14** 267, 1937, (b) The Mammalian Red Cell and the Properties of Haemolytic Systems, in Chambers, R Protoplasma-Monographien, Berlin, Gebruder Borntraeger, 1934, vol 6

15 Price-Jones, C Red Blood Cell Diameters, London, Oxford University Press, 1933

16 von Boros, J Die Behandlung der Anamien, *Ergebn d inn Med u Kinderh* **42** 635, 1932

17 Daland, G A, and Worthley, K The Resistance of Red Blood Cells to Hemolysis in Hypotonic Solutions of Sodium Chloride, *J Lab & Clin Med* **20** 1122, 1935

TABLE 3—Average Values for Venous Blood, Average Dimensions and Average Relative Osmotic Pressure for Mean Hypotonic Hemolysis of Various Types of Erythrocytes

Type of Erythrocyte	Venous Blood					Dimensions of Erythrocytest							
	Number of Erythrocytes per Microns ³	Erythrocytes, Millions per Cu Mm	Hemo globin, Gm per 100 Gc *	Erythrocytes, Volume %	Mean Corpuscular Hemoglobin Concentration %	V _o Microns ³	D _o Microns	T _o Microns	S _o Microns ²	V _s Microns ³	$\frac{V_s - V_o}{V_o}$	V _h	P _h
Hypochromic anemia	8	3.36	6.2	21.1	25.5	63.7	7.03	1.63	114.0	114.6	80.3	86.0	0.363
Normal human being	5	4.85	14.5	41.1	32.4	85.7	7.18	2.11	128.3	136.6	59.5	75.0	0.395
Dog	5	6.76	15.9	48.1	33.0	66.1	6.45	2.01	106.3	103.1	57.1	62.3	0.440
Hemolytic jaundice	6	3.42	11.4	29.1	36.1	84.4	6.88	2.28	122.9	128.0	51.7	48.0	0.505
Rabbit	5	3.97	9.4	30.7	30.7	70.9	6.22	2.34	106.7	103.4	46.1	43.4	0.530
Pig	4	8.23	14.6	45.3	32.3	51.9	5.47	2.21	85.3	74.2	42.9	38.5	0.560
Sheep	4	9.39	11.3	35.5	33.0	35.4	4.14	2.63	61.4	45.1	27.4	30.0	0.620

* 15.6 Gm equals 100 per cent

† V_o indicates mean corpuscular volume, D_o, mean corpuscular diameter, T_o, mean corpuscular thickness ($\frac{4}{\pi} \frac{V_o}{D_o^2}$), S_o, mean corpuscular surface ($\pi D_o T_o + \frac{\pi D_o^2}{2}$), V_s, volume of sphere with surface S_o $\frac{V_s - V_o}{V_o}$ percentage increase in volume of discoidal form (V_s) over discoidal form (V_o), V_h, $\left[\frac{1(100 - 51)}{P_h} + 51 \right] - 100$ percentage increase in volume of discoidal form at relative osmotic pressure for mean hemolysis P_h relative osmotic pressure for mean hemolysis

responded sufficiently closely to that in hypotonic solution of sodium chloride, so that a 1 per cent solution of sodium chloride could be considered approximately isotonic with undiluted oxalated plasma

In chart 2 are plotted the results of calculations of the value $\frac{V_s - V_o}{V_o}$ based on data obtained from individual observations on the erythrocytes of thirty-seven samples of blood. Each value is plotted as the ordinate against the relative osmotic pressure observed to produce 50 per cent hemolysis of the particular sample of erythrocytes as the abscissa. Inspection of the points shown in chart 2 suggests that they fall in general along the extrapolation of the observed curve of percent-

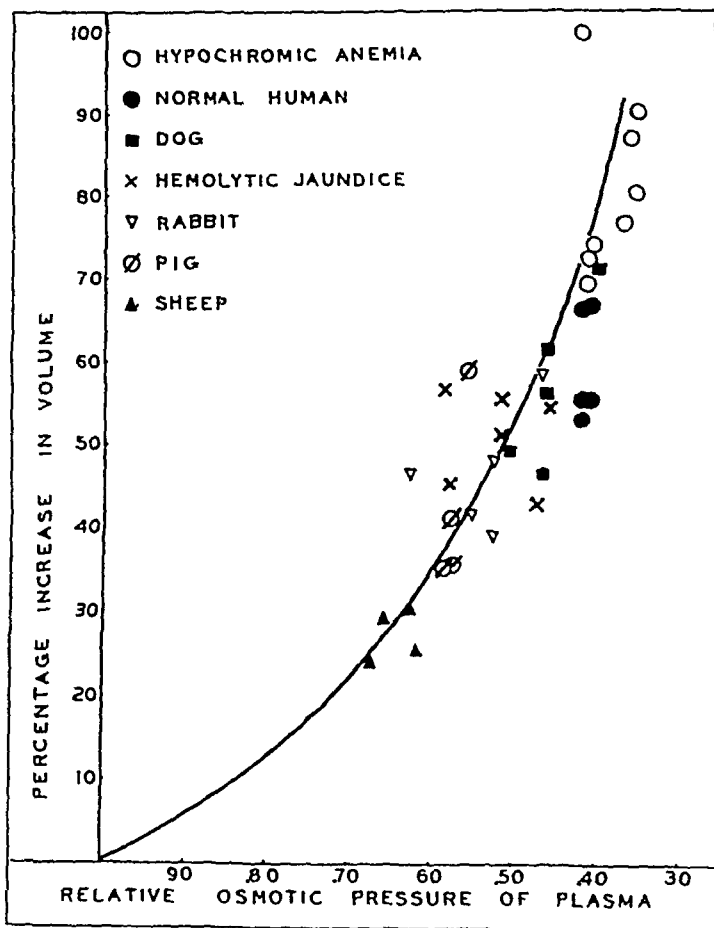


Chart 2—The percentage increase in discoidal volumes of samples of individual erythrocytes, calculated from formula $\frac{V_s - V_o}{V_o}$, compared with the percentage increase in discoidal volumes at relative osmotic pressures for mean hemolysis, derived by extrapolation of the average curve for equilibrium volumes shown in chart 1

tage increase in volume, which is identical with that shown as a solid line in chart 1. In table 3 are presented the average values of $\frac{V_s - V_o}{V_o}$ for each of the various types of erythrocytes, arranged in the order of increasing susceptibility to hypotonic hemolysis. This order was paralleled by the values of $\frac{V_s - V_o}{V_o}$ and, except for the normal human erythrocyte, the numerical correspondence with the percentage increase in equilibrium volume (V_h) at the relative osmotic pressure for mean hypotonic hemolysis (P_h) was reasonably good.

Correlation of Apparent Differences in Time of Hemolysis of Erythrocytes with Differences in Discoidal Form—In dealing with the rate of entry of water into spherical cells in hypotonic solution, measurement of the increase in volume at any moment can be made by determination of the diameter. Because this method is obviously not applicable to nonspherical cells, such as erythrocytes, since the work of Hamburger, the appearance of hemolysis has been applied to determinations of the permeability of erythrocytes. Jacobs¹⁰ has pointed out the various limitations of this method, including the difficulty of using hemolysis as the indicator of increase in volume for nonspherical cells which may undergo considerable or different increases in volume before the surface begins to be extended. He has presented a formula for expressing the rate of entry of water based on the assumption that the surface of the erythrocyte does not increase during the swelling process. Since this is precisely the assumption involved in Gansslen's explanation of differences in susceptibility to hemolysis when osmotic equilibrium is established, further evidence of its validity might be obtained by study of the time required for hemolysis of different types of erythrocytes. On the assumption that differences in this time are due not to differences in permeability but to differences in the value $\frac{V_s - V_o}{V_o}$, a relationship to the increase in volume possible without change in surface might be apparent.

TABLE 4—Time Required for 75 Per Cent Hemolysis of Various Types of Erythrocytes in a 0.02 Molar Solution of Sodium Chloride

Species	Observed Time, Seconds*	Calculated Time, Seconds	
		$k = 0.3758 \times 10^{-4}$	$k = 0.39 \times 10^{-4}$
Man	8.35	8.35	6.56
Dog	6.10	5.15	4.76
Rabbit	3.00	3.53	3.10
Pig	3.00	2.75	2.63
Sheep	1.90	1.91	1.90

* After Jacobs¹⁰. The figures in boldface type are the basis for the calculations of the respective values of k .

Jacobs¹⁰ has presented data on the time required for 75 per cent hemolysis of erythrocytes of several types of animals after the sudden mixing of a small amount of defibrinated blood with a large volume of two-hundredths-molar solution of sodium chloride. His studies included erythrocytes for which we have pertinent data, namely, those of man, dog, rabbit, pig and sheep. The respective times observed by Jacobs for 75 per cent hemolysis of the erythrocytes of these species at 20 C are given in table 4.

From these data, according to Jacobs' formula for the rate of entry of water, the permeability constants of the human and the sheep cell, respectively, were calculated as follows:

$$k = \frac{p_o V_o}{P^2 A t} \ln \frac{p_o V_o - P V_o}{p_o V_o - P V_s} - \frac{V_s - V_o}{P A t}$$

utilizing our values for the cell dimensions. In Jacobs' formula k is the permeability constant, t , the time in seconds required for 75 per cent hemolysis, A , the constant surface of the erythrocyte, V_o and p_o are the initial volume and osmotic pressure, respectively, of the erythrocyte in defibrinated blood (considered isotonic with 1 per cent solution of sodium chloride), V_s and P are, respectively, the spherical volume and the constant external osmotic pressure (two-hundredths-molar sodium chloride). Determination of the value of k for the human cell gave 0.3758

$\times 10^{-4}$, and for the sheep cell 0.39×10^{-4} . Using each value, the times required theoretically for hemolysis of the other types of erythrocytes were then determined by means of Jacobs' formula and are shown in table 4 for comparison with the actual times observed by Jacobs.

Inspection of the data given in table 4 suggests that the theoretical values are at least of the order of magnitude to be expected on the basis of the assumption that differences in shape may account for differences in the time required for hemolysis. Jacobs' observations, as well as our own, are merely averages for each type of erythrocyte. Better correspondence might have resulted had the experiments been made by one observer on the same samples of each type of blood. It is suggested that differences in the rate of penetration of water do not exist but that in the absence of more direct evidence the apparent differences in the times of hemolysis of different types of erythrocytes may be explained by differences in the forms of the erythrocytes.

COMMENT

The data in table 2 suggest that the percentage increases in volume of erythrocytes of different susceptibilities to hypotonic hemolysis are not significantly different. Nevertheless, the question arises whether, despite appearances to the contrary, sufficient differences exist to account entirely for the differences in susceptibility to hemolysis. In order to settle this question, theoretical percentage increases in volume of the various types of erythrocytes were calculated on the assumption that the greater the susceptibility to hemolysis of any type of erythrocyte, the greater would be the percentage increase in its equilibrium volume.

To effect this, it was first necessary to have a mathematical expression describing the average observed percentage increases in volume shown in table 2. For this purpose it is immaterial whether the effects observed are associated with an osmotically inactive cell component¹⁸ or with "leakage" of osmotically active substance out of the erythrocyte.¹⁹ The equation used by Lucké and McCutcheon,¹⁸ $V_e = \frac{P_o(V_o - b)}{P_e} + b$, expresses the law of Boyle-van't Hoff as applied to cells containing a nonosmotically active fraction. As applied to our experiments, P_o and V_o stand, respectively, for the relative osmotic pressure of the undiluted oxalated plasma and the volume occupied by the erythrocytes in this plasma. The constant, b , represents the osmotically inactive volume of the erythrocyte. The theoretical values for V_e and P_e giving the best approximation to the average observed values (table 2) were obtained by using a value for b of 51 per cent of V_o . With this value, the curve shown in chart 1 was plotted and extrapolated beyond the range of the observed values according to the formula $V_e = \left[\frac{1(100-51)}{P_e} + 51 \right] - 100$. Since the result desired is the

¹⁸ Lucké, B., and McCutcheon, M. The Living Cell as an Osmotic System and Its Permeability to Water, *Physiol Rev* **12** 68, 1932.

¹⁹ Ponder, E. The Kinetics of Hemolysis, *Physiol Rev* **16** 19, 1936.

percentage increase in volume, the original volume occupied by the erythrocytes (V_o) was taken as 100, and the relative osmotic pressure of the undiluted plasma (P_o) was taken as 1

By the methods previously described, approximately 50 per cent of the sheep corpuscles were found to be hemolyzed in a concentration of saline solution or of oxalated plasma of 0.62 (table 3). In this concentration, as shown by inspection of the solid curve in chart 1, the apparent average increase in volume of all types of erythrocytes was 30 per cent. It was then assumed, however, that the increased resistance to hemolysis of the other types of erythrocytes was due *entirely* to proportionately smaller increases in volume in oxalated plasma of 0.62 concentration but that an equal (30 per cent) increase in volume would be attained at the respective lower concentrations of plasma causing 50 per cent hemolysis of each type of erythrocyte. By substituting for V_e the value of 30 and for P_e the respective values for the relative osmotic pressure causing 50 per cent hemolysis of the various types of erythrocytes (table 3), the respective theoretical values for b were found by solution of the equation $V_e = \left[\frac{1(100-b)}{P_e} + b \right] - 100$

The hypothetical values of b thus found were used, and illustrative curves for the erythrocytes of patients with hemolytic jaundice and hypochromic anemia, respectively, were plotted in broken lines as shown in chart 1. The theoretical value of b for hemolytic jaundice was 69.4, that for hypochromic anemia, 82.9 per cent of V_o . Inspection shows at once that these curves fall outside the limits of the observed data given in table 2 and represented by the vertical lines intersecting the solid curve in chart 1. Similar families of curves could, of course, be plotted by taking any other of the types of erythrocytes as the basis of comparison. The position of the curves with respect to the curve for observed swelling would be different, but some of the curves would fall outside the limits of the observed data.

These considerations clearly indicate that differences in osmotic effects cannot explain the observed differences in resistance to hemolysis. Although slight differences in the percentage increase in volume of the different types of erythrocytes may exist because of slight differences in individual values for b , it appears probable that a given mass of erythrocytes of any of the types studied takes up from a given concentration of diluted plasma very nearly the same amount of liquid. Likewise, from a recent investigation of the osmotic properties of the erythrocytes of four species (sheep, ox, rabbit and man) after conversion into a spherical form without change in volume, Ponder³ concluded that differences in water content and in the extent to which the erythrocytes behave as "perfect osmometers" play only a minor part in determining differences in susceptibility to hemolysis. Ponder's

observations, however, were made on erythrocytes converted into a spherical form without change in volume by the addition of lecithin. Consequently, the experimental conditions do not necessarily correspond to those obtained when erythrocytes are freely suspended in hypotonic plasma or saline solution.

Whether the discoidal form of the erythrocyte is inherent in the construction of the cell envelop (to use Ponder's^{14b} simile, "as a Rugby

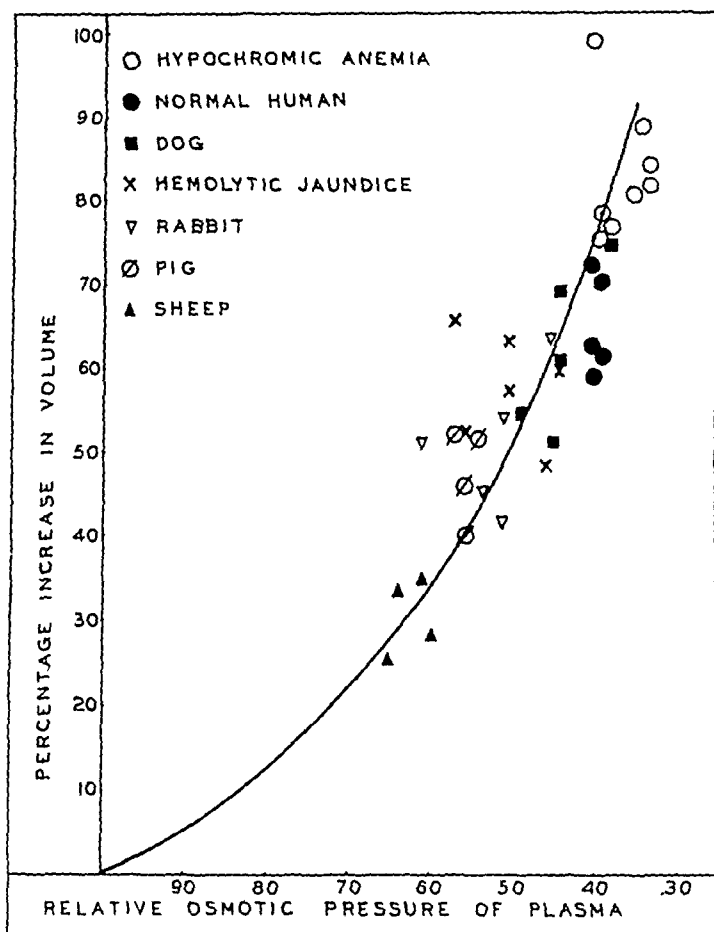


Chart 3—The percentage increase in discoidal volumes of samples of individual erythrocytes, calculated as a function of their respective *discoidal diameter-thickness ratios*, relative to that of the average sheep erythrocyte. These values are plotted against the respective relative osmotic pressures for mean hemolysis of each sample of erythrocytes. The curve is that shown in chart 1.

football is different from an Association football") or whether the discoidal form is the resultant of forces acting on an envelop of uniform extent, would influence the accuracy of calculations based on Gansslen's hypothesis. The question cannot at present be definitely answered. Microscopic observations, however, apparently indicate that in swelling the erythrocyte becomes spherical.

It is certain that after the erythrocyte has become spherical a further increase in volume will cause extension or stretching of the cell membrane. If a geometric explanation of differences in susceptibility to hypotonic hemolysis is to obtain, it is necessary to suppose that the release of the cell contents containing hemoglobin is brought about by physical effects on the cell membrane. That physical injury to the membrane may cause a release of hemoglobin, though sometimes denied,²⁰ has been proved by microdissection²¹ and can be easily

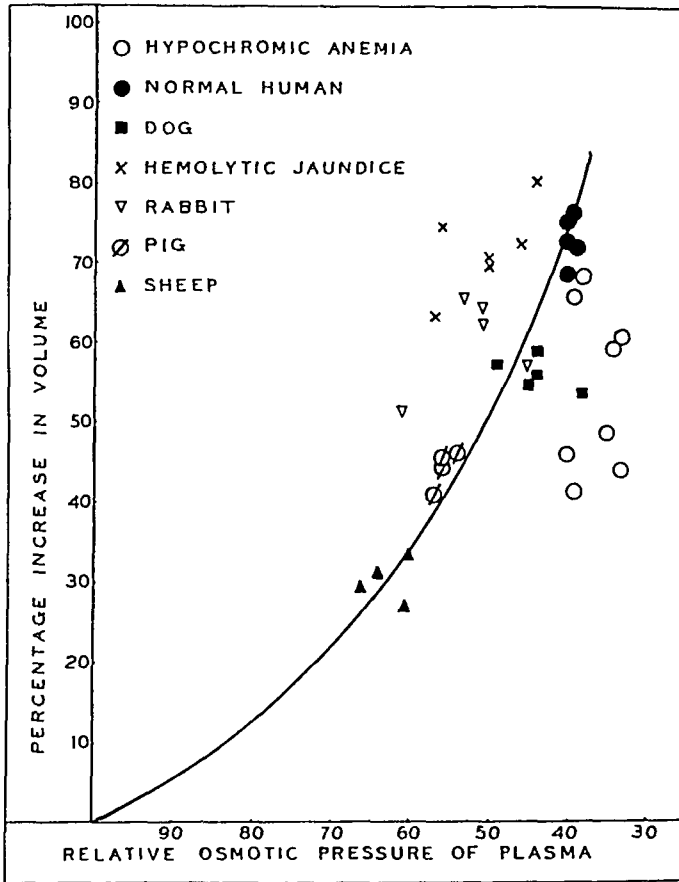


Chart 4—The percentage increase in discoidal volumes of samples of individual erythrocytes, calculated as a function of their respective *discoidal volumes* relative to that of the average sheep erythrocyte. These values are plotted against the respective relative osmotic pressures for mean hemolysis of each sample of erythrocytes. The curve is that shown in chart 1.

demonstrated by grinding oxalated blood with fine emery powder in a mortar for a few minutes, with adequate provision for prevention of

20 Rockwood, R. Physicochemical Aspects of Hemolysis. II. An Ultra-microscopic Study of Hemolysis, *J Lab & Clin Med* **10** 19, 1924.

21 Seifriz, W. The Physical Properties of Erythrocytes, *Protoplasma* **1** 345 1927.

heating and evaporation. After centrifugation of the contents of the mortar, the supernatant plasma will be found to contain hemoglobin free from erythrocyte debris. The properties and behavior of the erythrocyte therefore seem to be consistent with a geometric explanation of differences in susceptibility to hypotonic hemolysis.

The difficulties of subjecting Gansslen's hypothesis to quantitative tests are obvious. It is fully realized that every step in the calculation

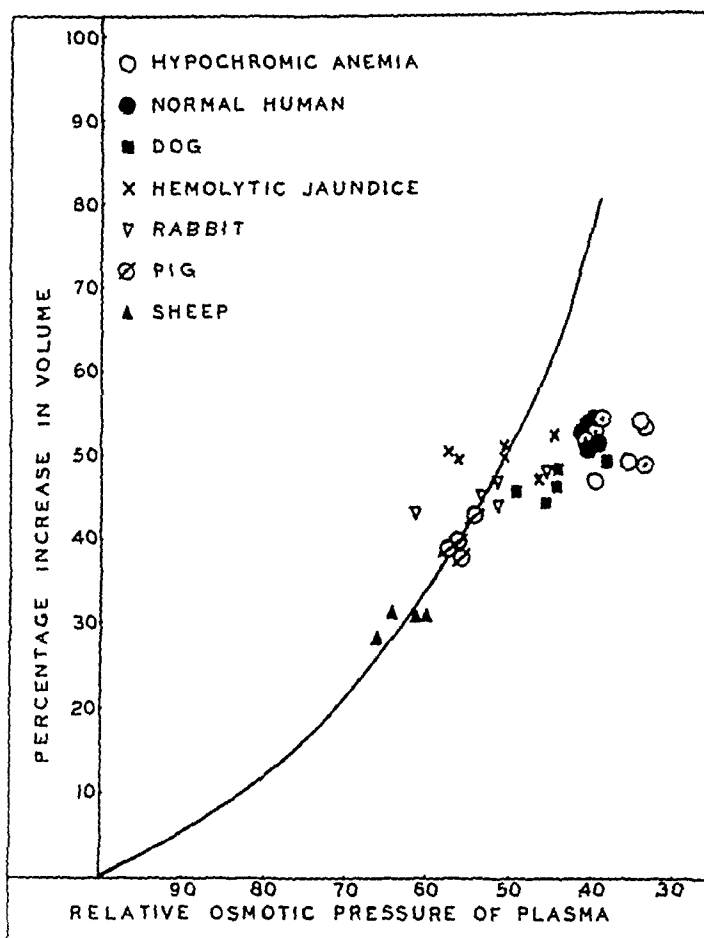


Chart 5—The percentage increase in discoidal volumes of samples of individual erythrocytes, calculated as a function of their respective *discoidal diameters*, relative to that of the average sheep erythrocyte. These values are plotted against the respective relative osmotic pressures for mean hemolysis of each sample of erythrocytes. The curve is that shown in chart 1.

of the value $\frac{V_s - V_o}{V_o}$ depends on approximations imposed by the experimental conditions rather than on accurate measurement of the erythrocyte. Values for V_o were obtained in oxalated plasma, whereas values for mean diameter (D_o) were obtained in dried smears. Because the precise shape of the erythrocyte is not known, it is obviously impossible to calculate exactly the surface of the erythrocyte at volume

V_o . Therefore, von Boros' ¹⁶ assumption of its resemblance to a right cylinder appears to be as satisfactory a method as any of obtaining at least a relative value for the mean corpuscular thickness and hence for the surface of the erythrocyte

A certain degree of correlation between mean susceptibility to hypotonic hemolysis and any measurement of the erythrocyte is to be expected if differences in its form are responsible for differences in susceptibility to hypotonic hemolysis. Thus, in charts 4 and 5 some correspondence with the curve for the equilibrium volume is observed for the relative percentage increases in volume which might be expected at the point of 50 per cent hemolysis of each *sample* of erythrocytes if such an increase were a function, respectively, of the original discoidal diameter or volume of the erythrocytes. In chart 3, in which the

TABLE 5—*Calculated Average Percentage Increase in Volume at Relative Osmotic Pressure for Mean Hypotonic Hemolysis*

Type of Erythrocyte	Values Relative to Sheep Erythrocytes as Function of					Absolute Values		
	V_o	D_o	S_o	D_o	T_o	$\frac{V_s - V_o}{V_o}$	V_h	P_h
Hypochromic anemia	54.0	51.0	55.6	82.2		80.3	86.0	0.363
Normal human being	72.6	51.9	63.1	64.2		59.5	75.0	0.395
Dog	56.0	46.7	52.1	61.4		57.1	62.3	0.440
Hemolytic jaundice	71.6	49.7	60.6	57.3		51.7	48.0	0.505
Rabbit	60.1	45.0	52.3	50.9		46.1	43.4	0.530
Pig	43.8	39.5	41.6	46.8		42.9	38.5	0.560
Sheep	30.0	30.0	30.0	30.0		27.4	30.0	0.620

V_o , D_o , T_o and S_o are the discoidal volume, diameter, thickness and surface, respectively, of the erythrocytes in isotonic plasma. For convenience the reciprocal of the T/D ratio of Haden ⁹ has been used. V_h , or $\left[\frac{1(100-51)}{P_h} + 51 \right] - 100$, indicates the percentage increase in discoidal volume at P_h . P_h indicates the relative osmotic pressure for mean hypotonic hemolysis.

relative values are based on the discoidal diameter-thickness ratio ²² of the various samples of erythrocytes, the correspondence is much better and seems to be as good as that obtained on the basis of the $\frac{V_s - V_o}{V_o}$ value shown in chart 2. The basis for computation of these relative values was the average sheep erythrocyte considered to have, from inspection of chart 1, an increase in volume of 30 per cent at a relative osmotic pressure of 0.62, the value for 50 per cent hemolysis. It is to be emphasized that, whereas the calculations based on the diameter, volume or diameter-thickness ratio give merely *relative* values here calculated with respect to the average sheep erythrocyte as a base, the expression $\frac{V_s - V_o}{V_o}$ is an attempt at an *absolute* value.

In table 5 the various types of erythrocytes are arranged in the order of increasing average susceptibility to hemolysis. The cor-

²² For convenience the reciprocal of the thickness-diameter ratio of Haden ⁹ is used.

respondence, both in order and numerically, of the $\frac{V_s - V_o}{V_o}$ values with the average values for the relative osmotic pressure causing mean hemolysis has been pointed out (tables 3 and 5). This order is likewise preserved by the percentage increases in volume relative to the sheep erythrocyte, calculated on the basis of the diameter-thickness ratio. On the contrary, in respect to correlations on the basis respectively, of original volume, diameter and surface, shown in table 5, there are two notable exceptions to this order which throw weight in favor of the significance of the *form* of the erythrocyte in determining its susceptibility to hypotonic hemolysis. The small discoidal volume of the erythrocyte of hypochromic anemia would place it just above the erythrocytes of the pig in table 5. On the basis of discoidal volume, the erythrocytes of hemolytic jaundice would be classed with normal human erythrocytes, on the basis of discoidal diameter, they would be placed between the erythrocytes of normal man and those of the dog. Correlations based on the discoidal surface of each type of erythrocyte also show that the erythrocytes of hypochromic anemia and those of hemolytic jaundice present exceptions. Placed in order of increase in volume as a function of discoidal surface, the erythrocytes of hypochromic anemia would come below, instead of above, the erythrocytes of normal man, the erythrocytes of hemolytic jaundice would come above instead of below the erythrocytes of the dog.

Thus, when susceptibility of the erythrocyte to hypotonic hemolysis is regarded as a function of the percentage difference between the original discoidal volume and the volume of a sphere of equal surface, the varied susceptibility to hemolysis of the erythrocytes of these different species and pathologic conditions can, to some extent, be anticipated.^{14a}

CONCLUSIONS

Our results suggest that differences in the susceptibility of various types of erythrocytes to hemolysis with hypotonic solution of sodium chloride are due largely to differences in form and not to differences in osmotic behavior.

The percentage increases in equilibrium volumes in hypotonic plasma of erythrocytes of widely different susceptibilities to hemolysis do not show significant differences.

Direct microscopic observations indicate that (a) hemolysis of a given type of erythrocyte is associated with the assumption of a spherical form in hypotonic plasma and that (b) the more susceptible the erythrocyte to hypotonic hemolysis, the less hypotonic the plasma necessary to cause the assumption of a spherical form.

An approximation to the percentage increase in volume necessary to cause hemolysis can be made by calculation of the percentage difference between the volume of the erythrocyte in isotonic plasma (V_o) and that of a sphere of equal surface (V_s)

In correlations of the *relative* degree of susceptibility to hypotonic hemolysis of a series of types of erythrocytes with their respective volume, diameter or surface in isotonic plasma, the erythrocytes of hypochromic anemia and of chronic hemolytic jaundice present exceptions

When these correlations are made on the basis of the diameter-thickness ratio or when *absolute* values are calculated according to the formula $\frac{V_s - V_o}{V_o}$, the erythrocytes of hypochromic anemia and of chronic hemolytic jaundice do not present these exceptions

Differences in the time necessary to cause hypotonic hemolysis of different types of erythrocytes may possibly be explained by difference in the percentage increase in volume of the discoidal form necessary to produce the spherical form in hypotonic solution

RETENTION AND UTILIZATION OF PARENTERALLY ADMINISTERED IRON

W M FOWLER, M D

AND

ADELAIDE P BARER, P H D

IOWA CITY

Parenterally administered iron has been used for many years in the treatment of anemia. Stockman,¹ in 1893, reported on the efficacy of this mode of administration and quoted many previous investigators who had found it to be of value, but from his own experience he concluded that a more rapid increase in the hemoglobin content could be obtained by oral administration. He stated, however, that the therapeutic activity of iron when given by this route was evidence that it was actually absorbed and utilized, a point which was being questioned at that time. This method of administration has been used by Witts,² by Barlow³ and Bullock⁴ in the anemia of tuberculosis and by Morse⁵ in the anemia of infants, as well as by numerous other investigators. All have recognized the fact that the amount of iron administered parenterally must be small because of its toxicity. More recently Heath, Strauss and Castle⁶ have reviewed the previous investigations and have presented evidence not only of the effectiveness but of the toxicity of iron when given by this route. They have shown that iron so administered to a group of seventeen patients produced a reticulocyte response as well as a rather rapid increase in the hemoglobin content of the blood and that 32 mg of iron administered parenterally is equivalent to 1,000

From the Department of Internal Medicine, the State University of Iowa

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1 Stockman, R. The Treatment of Chlorosis by Iron and Some Other Drugs, *Brit M J* **1** 881 and 942, 1893

2 Witts, L J. Treatment of Anemias, *Brit M J* **1** 100 (Jan 21) 1933

3 Barlow, W J, and Cunningham, R L. Effects of Hypodermic Injection on the Secondary Anemia of Chronic Pulmonary Tuberculosis, *J A M A* **57** 1435 (Oct 28) 1911

4 Bullock, E S, and Peters, L S. The Use of Hypodermics of Citrate of Iron in the Secondary Anemia of Tuberculosis, *J A M A* **57** 1428 (Oct 28) 1911

5 Morse, J L. The Treatment of Anemia in Infancy with Citrate of Iron Administered Subcutaneously, *J A M A* **53**.107 (July 10) 1909

6 Heath, C W, Strauss, M B, and Castle, W B. Quantitative Aspects of Iron Deficiency in Hypochromic Anemia. The Parenteral Administration of Iron, *J Clin Investigation* **11** 1293, 1932

mg administered by mouth. In only two of the seventeen patients did the hemoglobin content fail to increase, and the average utilization of the iron in hemoglobin formation in fourteen of the seventeen patients was 96 per cent, with extremes of 69 and 154 per cent. They concluded that the amount of iron given parenterally corresponds closely to the amount of iron gained in the circulating hemoglobin.

We have presented studies showing the retention and utilization of orally administered iron as determined by studies of the iron balance and wish to present similar balance studies of patients receiving iron parenterally.

TABLE 1—*Clinical Features*

Patient	Age	Sex	Diagnosis	Clinical Features
1	45	F	Hypochromic anemia, hemorrhage	Pale and anemic for eighteen years, menstrual periods always profuse, several severe uterine hemorrhages, biopsy showed only hyperplastic endometritis
2	43	F	Hypochromic anemia, hemorrhage, pregnancy	Profuse menses for several years, one severe uterine hemorrhage and one post partum hemorrhage, pale since ninth and last pregnancy
3	52	F	Hypochromic anemia, hemorrhage	Pale and weak for four years, symptoms began with severe climacteric bleeding, several profuse hemorrhages from hemorrhoids, dysphagia
4	40	F	Hypochromic anemia, idiopathic (?), pregnancy (?)	No history of excessive loss of blood, eleven pregnancies

TABLE 2—*Hematologic Data**

Patient	Hemo- globin, Per centage	Hematocrit Reading, Per centage	Erythro- cytes, Per centage	Color Index	Volume Index	Saturation Index	Gastric Acidity	Basal Metabolic Rate
1	55	77	77	0.71	1.00	0.71	0	+10
2	49	63	80	0.61	0.78	0.77	Low	-11
3	39	45	60	0.65	0.75	0.86	0	-4
4	55	72	73	0.75	0.98	0.76	0	+4

* The percentages and indexes are based on the normal values and tables of Osgood (A Textbook of Laboratory Diagnosis, ed. 2, Philadelphia, P. Blakiston's Son & Co., 1935, p. 420).

METHOD

These metabolic studies were carried out on patients with a microcytic hypochromic type of anemia. A brief summary of the clinical and hematologic features is given in tables 1 and 2. The details of the methods employed in these experiments have been given in a previous report.^{7a} Three diets were arranged for each patient according to the caloric requirement and were alternated during the period of study. The patients received these diets for a three day period of adjustment.

7 (a) Fowler, W. M., and Barer, Adelaide P. Retention and Utilization of Orally Administered Iron, *Arch. Int. Med.* **59**: 561 (April) 1937, (b) Retention and Utilization of Small Amounts of Orally Administered Iron, *ibid.* **59**: 1024 (June) 1937, (c) Barer, Adelaide P., and Fowler, W. M. Influence of Copper and a Liver Fraction on Retention of Iron, *ibid.* **60**: 474 (Sept.) 1937.

before observations were begun. The iron balance was then ascertained for a control period in which the intake of iron was from the food alone. Thus, as well as the subsequent periods during which medicinal iron was administered, was of six days' duration. The intake and excretion of iron for each period were determined, and from these data was calculated the daily iron balance. Complete data for the nitrogen and phosphorus balances were determined for all the patients.

One-tenth gram of green iron and ammonium citrates was administered intramuscularly at daily intervals. The iron content of this preparation was ascertained by analysis of representative samples from each lot, and from this analysis and from the number of intramuscular injections was determined the amount of medicinal iron each patient received. Two patients were given 3 Gm of iron and ammonium citrates per day by mouth after receiving iron intramuscularly for twenty-four and eighteen days, respectively.

Determinations of the hemoglobin content, made by the Newcomer method, erythrocyte and reticulocyte counts and hematocrit readings were made on alternate days for all the patients.

A portion of the specimen of stool of patient 4 for the second period was lost, so that no balance studies could be made for that period. The patient received the medicinal iron continuously, however, so that the determinations of hemoglobin and erythrocytes were still of value.

RESULTS

The results of the studies of the nitrogen, phosphorus and iron balances are given in table 3, and table 4 presents a summary of the data on the iron retention of each patient. It will be noted in these tables that the retention of iron was much greater during the periods in which intramuscular injections of iron were being given than it was during the control periods. Patient 1 retained a total of 152.1 mg of iron and received only 139.7 mg by intramuscular injection, so that all medicinal iron was retained as well as a portion of the dietary iron (table 5). The same feature is true for patient 2, who retained 167.82 mg of iron, although only 139.7 mg of medicinal iron was administered. The control period for this patient showed a loss of 5.05 mg of iron per day, but it is obvious that a portion of the dietary iron was retained in the remaining periods. In patient 3 there was a retention of 303.89 mg from the administration of 304.8 mg, so that over 99 per cent of the medicinal iron was retained and the diet was apparently just sufficient to keep the patient in balance. Owing to the loss of one specimen for patient 4, the data on iron retention cannot be subjected to analysis.

These results indicate that the entire amount of intramuscularly administered iron is retained by the body.

Iron was administered by mouth to patients 3 and 4 after they had received iron intramuscularly for twenty-four and eighteen days, respectively. Patient 3 received a total of 6,212.4 mg of iron during two balance periods and retained 2,187.42 mg, a retention of 35 per cent of the amount administered. Patient 4 retained 47 per cent of the orally administered iron during the same length of time. These results are

TABLE 3—*Nitrogen, Phosphorus and Iron Balances*

Patient	Period	Nitrogen, Gm			Phosphorus, Gm			Iron, Mg			Red Blood Cells, Millions per Cu Mm		Hemato crit Reading, Percentage	Hemo globin, Gm per 100 Cc
		Average Daily Intake	Average Daily Excretion	Average Daily Balance	Average Daily Intake	Average Daily Excretion	Average Daily Balance	Average Daily Intake	Average Daily Excretion	Average Daily Balance				
1	1	9 78	9 35	+0 43	1 44	1 20	+0 24	11 89	11 78	+ 0 11	3 83	31 5	7 890	
	2	9 79	8 95	+0 84	1 44	1 19	+0 25	22 47	10 85	+ 11 62	4 15	31 0	7 625	
	3	9 79	8 66	+1 13	1 45	1 17	+0 28	24 59	10 86	+ 13 73	4 15	33 5	7 800	
2	1	9 78	9 99	-0 21	1 44	1 57	-0 13	11 89	16 93	- 5 05	3 98	27 0	7 015	
	2	10 41	8 81	+1 60	1 50	1 12	+0 38	24 63	10 58	+ 14 06	3 99	28 0	7 100	
	3	10 41	8 49	+1 92	1 49	1 21	+0 28	22 52	8 60	+ 13 92	3 55	32 0	7 275	
3	1	9 79	8 89	+0 90	1 45	1 23	+0 22	11 86	14 00	- 2 14	3 01	19 0	5 645	
	2	9 83	7 55	+2 28	1 45	1 41	+0 04	24 59	18 72	+ 5 87	3 38	20 0	5 450	
	3	9 79	8 54	+1 25	1 44	1 24	+0 20	24 29	8 26	+ 16 03	3 64	21 0	5 450	
	4	9 83	8 56	+1 27	1 45	1 38	+0 07	24 59	8 10	+ 16 49	3 63	21 5	5 595	
	5	9 83	9 40	+0 43	1 45	1 40	+0 05	24 59	12 33	+ 12 26	3 77	23 0	5 355	
	6*	10 11	8 59	+1 52	1 45	1 18	+0 27	517 70	237 10	+280 60	3 86	26 5	6 595	
	7*	10 11	9 24	+0 87	1 45	1 76	-0 31	517 70	433 73	+ 83 97	4 47	31 0	7 625	
4	1	9 77	9 88	-0 11	1 44	1 30	+0 14	11 59	10 08	+ 1 52	3 62	31 0	7 800	
	2	9 80			1 45			24 56			3 89	29 0	7 015	
	3	9 84	9 18	+0 66	1 45	1 17	+0 29	24 60	12 31	+ 12 29	3 87	30 0	7 365	
	4	9 85	9 41	+0 44	1 44	1 27	+0 17	24 59	19 12	+ 5 47	4 30	31 0	7 370	
	5*	10 14	10 43	-0 29	1 44	1 25	+0 19	517 70	284 08	+233 63	4 43	33 0	8 905	
	6*	10 14	10 25	-0 11	1 44	1 40	+0 04	517 70	263 69	+254 01	4 13	35 0	10 940	

* The patient received iron and ammonium citrates orally, $\frac{1}{2}$ Gm per day

similar to those obtained for a group of ten patients who received the same amount of iron by mouth and in whom the iron retention varied from 14 to 71.4 per cent, with an average retention of 32.6 per cent.^{7a} It is apparent, therefore, that patients 3 and 4 reacted similarly to the same amount of orally administered iron as did other patients.

Our results differ from those of other investigators in respect to regeneration of hemoglobin. Both in animals⁸ and in human beings⁶ it has been reported that iron is used almost quantitatively in hemoglobin formation. The amount of iron that we have injected has been relatively small, but we have shown that it has been retained almost completely. In spite of this retention, there was no regeneration of hemoglobin in three of the four patients, and only an exceedingly slight increase was

TABLE 4—Retention of Iron

Patient	Iron Balance, Mg						
	Control Period	Period 1	Period 2	Period 3	Period 4	Period 5	Period 6
1	+0.11	+11.62	+13.73				
2	—5.05	+14.06	+13.92				
3	—2.14	+ 5.87	+16.03	+16.49	+ 12.26	+280.60*	+83.97*
4	+1.52		+12.29	+ 5.47	+233.63*	+254.01*	

* The patient was receiving iron and ammonium citrates by mouth.

TABLE 5—Total Retention of Iron

Patient	Total Iron Received in Diet, Mg	Total Iron Received Intramuscularly, Mg	Total Iron Retained, Mg
1	142.64	139.70	152.10
2	143.20	139.70	167.82
3	283.58	304.80	303.89

noted in patient 2. Although the first two patients received iron for only twelve days, it seems that some regeneration should have been apparent within that length of time. Patients 3 and 4 received iron for twenty-four and eighteen days, respectively, with no regeneration of hemoglobin, and the duration of treatment cannot be criticized in these cases.

In order to determine whether the patients were capable of regenerating hemoglobin under more favorable conditions, iron and ammonium citrates was administered orally to patients 3 and 4 in doses of 3 Gm per day. Under these conditions a prompt and rapid hemoglobin response was obtained. Patient 3 gained 2.27 Gm of hemoglobin per hundred cubic centimeters of blood in twelve days, an increase of 0.189 Gm per day. Patient 4 gained 3.37 Gm during the same length of time,

⁸ Whipple, G. H., and Robschert-Robbins, F. S. Iron and Its Utilization in Experimental Anemia, *Am J M Sc* **191** 11, 1936.

which was an increase of 0.28 Gm per day. This is a more rapid gain than was obtained with the use of the same amount of orally administered iron in previously reported cases.^{7a} It indicates that these patients were capable of regenerating hemoglobin under suitable conditions and that the lack of response to iron administered intramuscularly was not due to the patient's inability to form new hemoglobin. The rapidity with which hemoglobin was formed when the iron was given by mouth may indicate that the tissue iron had been restored to normal by the intramuscular injections and as a result the response to the oral administration was more rapid than it would have been had the same amount of iron been given by mouth at the onset of treatment. Hare⁹ has reported similarly on a patient who received iron intramuscularly for nineteen days without benefit but who showed immediate and marked improvement when iron and ammonium citrates was given by mouth.

Although the hemoglobin response to iron administered intramuscularly was negligible in all cases, it will be noted that the erythrocyte count and the hematocrit reading increased for all but patient 2. An extremely slight reticulocyte response was obtained, 3.2 per cent for patient 3 being the highest reading. For the other patients the highest values were 1.4 and 1.4 per cent, respectively.

CONCLUSIONS

These results show that iron injected intramuscularly in the form of iron and ammonium citrates is retained by the body. It was expected under these circumstances that hemoglobin regeneration would follow, but this did not occur. That this lack of hemoglobin response is not due to an inability on the part of the particular patient to regenerate hemoglobin is shown by the rapid response of two of the patients who subsequently received iron by mouth. The reports of other investigators have shown that hemoglobin regeneration does ensue, both in animals and in human beings, after the intramuscular or the intravenous injection of iron, and we are at a loss to explain the almost complete absence of response in these patients. The dose which we employed, 0.1 Gm of green iron and ammonium citrates, is somewhat smaller than that which has been recommended. Heath⁶ administered the equivalent of 8 mg of iron intramuscularly to five patients and noted a slight hemoglobin response within from ten to eighteen days, and when 16 mg of iron was given to two patients for ten days, the increase in hemoglobin was 3 and 8 per cent, respectively. The average amount of iron which we gave was 12.3 mg per day. Although it is dangerous to draw extensive conclusions in respect to hemoglobin formation from such a small series

9 Hare, D. Treatment of the Anemias, *Brit M J* 1 100 (Jan 21) 1933

of patients, we did not find this amount of iron to be of value in the treatment of anemia, in spite of the fact that all the iron was retained by the body. It has been assumed that an excessive amount of iron may have some stimulating effect aside from its direct use in hemoglobin formation. Such results as we have obtained, when compared with the excellent results reported with 32 mg. of iron administered intramuscularly, may again raise this question. We do not, however, agree with a statement that parenterally administered iron can be quantitatively recovered in new-formed hemoglobin.

SUMMARY

Our results indicate that iron administered intramuscularly is retained by the body, but in the doses here employed it is not utilized in the formation of hemoglobin. The oral administration of iron appears to be more efficient in the treatment of hypochromic anemia.

CRITICAL ANAPHYLACTIC SHOCK

DURING TREATMENT FOR HAY FEVER RECOVERY AFTER THREE
INTRACARDIAC INJECTIONS OF EPINEPHRINE

STANLEY J JOYCE, M D

DETROIT

The tragedy of sudden death due to anaphylaxis is its unnecessary occurrence. A fatality which results from a purely optional treatment is difficult to reconcile, that a patient would have lived had such a procedure been omitted is not a consoling thought. Too often death has been caused by a prophylactic measure intended to protect the patient from some disease which he might have escaped even without treatment, as by the use of antitetanus serum. The fatal treatment may have been given to relieve symptoms of a disease not in itself serious, such as hay fever, or the reaction may have followed an error or accident in treatment. Furthermore, most of these tragedies could have been averted with immediate and adequate care during the reaction.

These reflections are well illustrated in the following case of a reaction due to ragweed antigen, in which death seemed imminent for about thirty minutes. The usual precaution of withdrawing the plunger of the syringe and the prompt application of a tourniquet did not avert the crisis. The situation was saved only after prompt, continuous and heroic action, including three intracardiac injections of epinephrine, the total administration of a large quantity of epinephrine (16 cc in one and one-half hours) and inhalation of oxygen for asphyxia resulting from acute pulmonary edema.

REPORT OF A CASE

C K, a Greek aged 40, married, was being desensitized with antigen of short ragweed for fall hay fever associated with severe asthma of ten years' duration. The first treatment of 200 units of pollen¹ (0.1 cc of 1:1,000 solution) was given on June 4, 1934. After the patient had arrived home a reaction with moderate asthma and urticaria developed, but cleared spontaneously in a few hours. No trouble from gradually increasing doses was then encountered until the ninth

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Whenever used in the text "epinephrine" is construed to mean a solution of epinephrine hydrochloride (1:1,000)

1 A unit of pollen, as used in this text, is the amount of nitrogen extracted from 0.001 mg of pollen with distilled water. The controversy over dosage of pollen is outside the scope of this paper.

treatment on July 6, when a similar but more severe reaction occurred during an expectant period of waiting at the office. After the application of a tourniquet to the arm above the site of the injection and the hypodermic administration of several small doses of epinephrine the reaction cleared completely in half an hour. Despite great care, similar reactions occurred after the eleventh and fourteenth treatments. During these reactions the patient exhibited marked cardiac irregularity.

Desensitization was then uneventful until the twenty-third treatment, given at 6 p. m. on August 16, when the same dose (0.28 cc of 1:25 solution) of antigen was administered as for the twenty-second treatment. Withdrawal of the plunger of the syringe did not show blood, but on withdrawal of the needle a small amount of blood appeared at the site of puncture, probably indicating penetration of a vessel and an impending reaction due to backseepage. By the time a tourniquet was adjusted severe asthma had developed. During the brief period taken to fill an already sterile syringe with epinephrine the reaction had progressed to an alarming degree. Epinephrine was immediately injected into both arms, and the patient was placed on a table. His condition rapidly became worse, he exhibited extreme dyspnea, marked cyanosis, failing pulse and loud bubbling râles (marked pulmonary edema). In less than a minute he became unconscious.² Evidences of respirations and pulses were absent. The patient stiffened into a generalized tonic convulsion. Without regard to specific location, epinephrine (1 cc) was given intracardially, and the patient responded slowly. Artificial respiration was instituted. The rescue squad of the fire department was called and arrived within ten minutes to give oxygen. Five and ten minutes after the first intracardiac injection of epinephrine was given a repetition was necessary. Meanwhile small amounts of epinephrine were being injected frequently into the arms, with massage of the sites of injection free from antigen. The indication for another dose was a relapse, with failing or cessation of the pulse and/or respirations. The patient remained unconscious for forty minutes, and the outlook appeared grave. The skin was purple, cold and clammy. The tongue was markedly edematous, completely filling the wide open mouth. When the patient's condition permitted it, the blood pressure was taken and was observed to be 180 systolic and 70 diastolic. The symptoms gradually cleared, and the patient responded irrationally, slapping away the oxygen mask, letting out loud cries, mumbling and tearing at his clothing. When consciousness was regained, he complained of itching of the soles of his feet, due to marked urticaria.

The patient's condition had been so critical that the tourniquet on the arm containing the antigen was not disturbed for fifty minutes and then only in small spurts, until completely released in about fifteen minutes. From 7 to 8 p. m. the patient vomited several times. About 7:15 p. m. he complained of cardiac pain and was given $\frac{1}{8}$ grain (81 mg.) of morphine sulfate hypodermically, with relief. During the next few hours the pulse rate ranged from 90 to 130, with variable quality and regularity.

Within an hour and a half of the onset of the reaction the patient's condition was sufficiently improved to permit his removal to a hospital for observation. He was apathetic, quiet and weak. At 8:30 p. m. 300 cc. of normal solution of sodium chloride was given intravenously. The temperature was 98.6 F, the pulse rate

² Mixtures of antigen and epinephrine, as used by Duke,⁵ or application of a pressure cuff before an injection of antigen as used by S. W. Insley (*The Control of Shock Following Hypodermic Medication*, J. A. M. A. **94** 765-767 [March 15] 1930), would likely prevent these reactions.

88 and the respiratory rate 28. A Murphy drip was instituted for twenty-four hours. For the next thirty-six hours the patient continued to have moderate asthma, which was controlled with twelve small doses of epinephrine or atropine and thereafter, when nausea had stopped, with ephedrine given orally. Small doses of morphine were given twice for comfort.

By the next day (August 17) the cyanosis had entirely cleared. There was moderate weakness. The soft tissues of the left side of the chest were emphysematous. The blood pressure ranged around 112 systolic and 84 diastolic (the patient had moderate arteriosclerosis). The maximum twenty-four hour values were as follows: The temperature was 99.6 F, the pulse rate was 110 and the respiratory rate was 38. The minimum twenty-four hour values were as follows: The temperature was 98.6 F, the pulse rate was 72 and the respiratory rate was 26. On the evening of August 18 the patient was discharged from the hospital.

The results of the treatments with ragweed antigen were nil, and the patient was compelled to migrate north because of severe asthma, which yielded to scarcely anything but epinephrine, and then only for brief periods. The patient was seen in July 1936 and was in his usual health.

CRITICAL AND FATAL REACTIONS TO POLLEN

The experience here encountered in the management of a critical reaction to ragweed antigen should prove profitable to other physicians.

Only two deaths and six serious reactions to injections of pollen antigen have been reported. Lamson³ reported death occurring during treatment with antigen of Bermuda grass which was injected into the area of the deltoid muscle. Two cubic centimeters of epinephrine was given (one dose only, none intracardially). Artificial respiration, dilatation of the rectum and administration of oxygen by the members of the fire department were of no avail, and the patient died within eight minutes.

The other report of a death following injections of pollen extract was found in a chart published by Waldbott⁴ listing nine fatal anaphylactic reactions (the rest were due to antiserum). The pollen reaction started one-half minute after the thirteenth injection of ragweed extract with death in two hours. "No effect from epinephrine" was noted.

A serious reaction to an injection of a pollen-epinephrine mixture was reported by Duke⁵. Coryza, cough and slight asthma developed followed by convulsions. The patient recovered two minutes after the application of a tourniquet, the injection of epinephrine into the other arm and the rubbing of ice on the chest, back and arms.

3 Lamson, R. W. So-Called Fatal Anaphylaxis in Man, with Especial Reference to Diagnosis and Treatment of Clinical Allergies, *J. A. M. A.* **93** 1775-1778 (Dec. 7) 1929.

4 Waldbott, G. L. Prevention of Anaphylactic Shock with Study of Nine Fatal Cases, *J. A. M. A.* **98** 446-449 (Feb. 6) 1932.

5 Duke, W. W. New Method of Administering Pollen Extract for Purpose of Preventing Reactions. Subcuticular Method, *J. A. M. A.* **94** 767-771 (March 15) 1930.

Restall and Burrage⁶ reported another serious reaction, which occurred after the sixteenth treatment with ragweed antigen in a boy of 18. With the start of the reaction 12 minims (0.74 cc) and later 6 minims (0.37 cc) of epinephrine was given. In about three hours the patient was normal after progressively experiencing drowsiness, weakness, slight twitching and burning of the eyes, symptoms of hay fever, headache, dizziness, blurring of vision, an attack of fainting, chill, tonic convulsions, Cheyne-Stokes respirations, sweating, flushing and amnesia concerning the reaction.

Will Walter⁷ reported a case of profound anaphylactic shock starting ten seconds after an injection of ragweed antigen in the same amount as that of a previous dose that had caused no reaction. The patient exhibited violent paroxysms of sneezing, cyanosis, asthma and cough productive of glairy mucus. "The pulse was hardly palpable. The blood pressure dropped to 80. This altogether alarming state lasted about two hours." No mention was made of restoratives.

Waldbott⁸ reported three critical reactions following injections of pollen extract. All the patients became dyspneic, cyanotic and unconscious, two became pulseless. One was given 0.5 cc of epinephrine subcutaneously at once, with a similar dose in three minutes and 1 cc intramuscularly in another three minutes. The second patient was given 1 cc of epinephrine at once and a similar dose subcutaneously later. No mention of restoratives was made in the third case.

That no more cases similar to these have been reported is surprising, for their occurrence is of commonplace knowledge. Unwanted notoriety, embarrassment and/or vulnerability of the technic employed probably account for the failure to report these experiences.

USE OF EPINEPHRINE IN OTHER ANAPHYLACTIC REACTIONS

An exhaustive review of the literature disclosed only a few instances of fatal anaphylaxis from all causes in which epinephrine was given intracardially. Three of these were reported by Lamson⁹. One followed the administration of antitetanus serum, another followed an intracutaneous test with ovomucoid (the patient was given "epinephrine even intracardially") and the third followed an intradermal test with

6 Restall, M. M., and Burrage, W. S. Unusual Type of General Reaction Following Treatment for Hay Fever, *New England J. Med.* **208** 543-544 (March 9) 1933.

7 Walter, Will. Inoculation Against Hay Fever. An Experience, Warning and Suggestion, *J. A. M. A.* **75** 670 (Sept. 4) 1920.

8 Waldbott, G. L., and Ascher, M. S. The Role of Accidental Puncture of Veins in the Production of Allergic Shock, *Ann. Int. Med.* **9** 1232-1239 (March) 1936. Waldbott, G. L. Systemic Reactions from Pollen Injections, *J. A. M. A.* **96** 1848-1851 (May 30) 1931.

9 Lamson, R. W. Sudden Death Associated with Injection of Foreign Substances, *J. A. M. A.* **82** 1091-1098 (April 5) 1924, footnote 3.

buckwheat The third patient received epinephrine intravenously, 0.5 cc at the site of the local reaction and 1 cc in the opposite arm, and intracardially In two cases epinephrine was given after the use of hemoplastin¹⁰ One of these patients "received epinephrine at once and again ten minutes later intracardially" In another case¹¹ the reaction followed an intracutaneous test with 0.05 cc of horse serum Epinephrine (0.3 cc) was injected into the arm, and further injections of epinephrine both subcutaneously and intracardially were made to "total over 1 cc" Employment of manual artificial respiration and the Drinker respirator was of no avail

In only three other instances of fatal anaphylaxis can any record of the intravenous administration of epinephrine be found One followed an injection of diphtheria antitoxin,¹² another followed an intracutaneous test with LePage's glue,¹³ and the third,¹⁴ followed an intravenous injection of normal horse serum In the third case 50 minims (3 cc) of epinephrine was given intravenously in five divided doses

Other than as mentioned in the foregoing paragraphs, there were no details as to the number of injections of epinephrine given, the amount or the routes employed

A number of severe but not critical anaphylactic reactions have been reported In these cases epinephrine was administered subcutaneously in amounts seldom totaling 3 cc Numerous reports of fatal anaphylaxis after injection of serum have made no mention of the administration of epinephrine In one case 20 drops was placed under the tongue, in a number of cases a single dose or several small doses were given subcutaneously and in many cases it was noted that epinephrine was administered, but no further details were cited

EPINEPHRINE GIVEN INTRACARDIALLY

Intracardiac injections of epinephrine have been given on numerous occasions for other than anaphylactic reactions Real interest in this pro-

10 DeLee, J. B. Fatal Anaphylaxis Following Hemoplastin, *J. A. M. A.* **82** 1564 (May 10) 1924 Neale, A. V. Acute Anaphylactic Shock Report of a Fatal Case, *Brit. J. Child Dis.* **27** 112-116 (April-June) 1930

11 Freedman, H. J. Acute Anaphylactic Shock Following Intracutaneous Test for Sensitivity to Horse Serum Report of a Fatal Case, *New England J. Med.* **212** 10 (Jan. 3) 1935

12 Bullowa, J. M., and Jacobi, Mendel. Fatal Human Anaphylactic Shock, *Arch. Int. Med.* **46** 306-315 (Aug.) 1930

13 Cooke, R. A. Studies in Specific Hypersensitiveness Constitutional Reactions, Dangers of Diagnostic Cutaneous Test and Therapeutic Injections of Allergens, *J. Immunol.* **7** 119-146 (March) 1922

14 Boughton, T. Harris. Anaphylactic Death in Asthmatics, *J. A. M. A.* **73** 1912 (Dec. 27) 1919

cedure developed about 1921, although credit is given to Latzko^{14a} for administering the first intracardiac injection to a human being in 1904. In the period of clinical trial "it was hailed as a miracle" as well as "a useless and dangerous operation." The procedure "occupied a stage of excited debate,"¹⁵ and skepticism was unreserved. Considerable controversy developed as to whether epinephrine should be given into the pericardial cavity, the cardiac muscle or a specific chamber. Injection into an auricle has obtained most favor. However, time should not be sacrificed in the selection of a site for injection.

Intracardiac injection of epinephrine is now definitely accepted as without an equal in all serious conditions in which there is any possibility of the patient's survival if the emergency can be passed. It is a specific antidote for anaphylactic reactions. Common indications are found in critical states of narcosis, including spinal and other forms of anesthesia, acute pulmonary edema, severe shock from injuries and acute respiratory or heart failure.

No authentic harm has ever been reported as a consequence of intracardiac injections in cases of emergency. Petit-Dutailis¹⁶ reported on over one hundred postmortem examinations in which it was almost impossible to find the intracardiac course of the needle. Large amounts of epinephrine and a number of injections can be given with reasonable impunity in a crisis. Error is more likely on the side of insufficiency. Dennis Crile¹⁷ reported on several cases in which a large quantity of epinephrine was given from 10 to 20 cc intravenously and from 5 to 10 cc intracardially. Paul Champlin¹⁸ gave a 10 cc dose of epinephrine intracardially to a patient who had collapsed during spinal anesthesia, recovery followed with no ill effects.

COMMENT

The dramatic effects of epinephrine are well known. The literature reveals an unbelievable paucity of reports on the use of the drug in severe and fatal anaphylactic shock. Many of these deaths can be directly charged to failure to use epinephrine at all or adequately. The

14a Latzko, cited by Bodon, C. The Intracardiac Injection of Adrenalin, *Lancet* **1** 586-590 (March 24) 1923.

15 Hyman, A. S. Resuscitation of the Stopped Heart by Intracardiac Therapy, *Arch. Int. Med.* **46** 553-568 (Oct.) 1930.

16 Petit-Dutailis, D. Intracardiac Injection of Epinephrine, abstr., *J. A. M. A.* **83** 720 (Aug. 30) 1924.

17 Crile, Dennis W. Resuscitation, Intracardiac Injections, *Surg., Gynec. & Obst.* **35** 772-775 (Dec.) 1922.

18 Champlin, Paul B. Resuscitation by Intracardiac Injection of Epinephrine Chlorid, *J. A. M. A.* **81** 202-203 (July 21) 1923.

following comment from an article published only a few years ago in *The Journal of the American Medical Association* by an eminent allergist is typical of the general lack of understanding of the adequate use of epinephrine "However, the value of epinephrine in extreme cases becomes somewhat doubtful if one considers the fact that death could not be prevented in two cases despite the administration of 1 cc and 1.5 cc of epinephrine" The statement, common in the literature, "that death occurred before adrenalin could be administered" is an admission that the physician did not have it available for ready use Even so, in some of these cases life might still have been saved if a supply could have been obtained reasonably soon Numerous reports of restoration after more than five minutes of cardiac standstill have been recorded

Undoubtedly there is greater recourse to the use of epinephrine than the literature discloses, yet an appalling condition, nothing short of criminal negligence, exists All this in spite of the fact that only little mention of authentic harm from its use is recorded, and no ill effects have followed massive doses, even when given intracardially

There is no standard dose of epinephrine, the requirements of the moment must be the guide The drug is best given subcutaneously in small doses (fractions of a cubic centimeter) to avoid unpleasant secondary effects and is repeated as necessary For the more severe reaction larger doses (1 to 1.5 cc) are indicated There should be no hesitancy in the use of the intravenous and intracardiac routes, with repetitions even of large doses, as indicated by the response of the patient Failure of epinephrine in an emergency can often be attributed to insufficient dosage A liberal quantity of the drug should be available to all physicians at all times for immediate use, and failure to anticipate the need of epinephrine in an emergency is unpardonable

The site of a parenteral injection should be chosen so that a tourniquet can be applied if necessary The experience here cited further emphasizes the dangers of self-administration of pollen antigen or of any parenteral treatment by any one unprepared to meet any emergency

SUMMARY

A critical reaction to ragweed antigen is reported, with recovery after three intracardiac injections of epinephrine (1 cc each), the subcutaneous injection of 13 cc of epinephrine in divided doses and the administration of oxygen

Although of common hearsay, reports of only two fatal and six critical reactions to pollen antigen can be found in the literature, and in none of these cases was epinephrine given intracardially

Timidity as to the number of injections or quantity of epinephrine to be given either hypodermically or intracardially in the present case would have resulted fatally

Reports of resort to the intracardiac administration of epinephrine are surprisingly lacking in articles on serious or fatal anaphylactic reactions

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COPPER AND IRON IN HUMAN BLOOD

V NORMAL ADOLESCENT CHILDREN FROM 14 TO 19 YEARS OF AGE

ADOLPH SACHS, M D

VICTOR E LEVINE, M D

AND

WILLIAM O GRIFFITH, B S

OMAHA

In a series of analyses previously made in this laboratory normal values for the copper and iron contents of the whole blood of adults were established¹ It was shown that while the average values for copper were practically the same, irrespective of sex, values for iron and hemoglobin were appreciably lower for women, so that separate standards of hemoglobin values for men and for women were advocated

In a more recent report² values were established for copper, iron and hemoglobin for normal children, ranging from new-born infants to children of 15 years The results in this series exhibited no sex variations, but the values fluctuated greatly with changes in age, especially in the first year of life It was suggested that for greater reliability in clinical interpretation a hemoglobin curve is preferable to a single standard for children

The present study was undertaken to complete the series of normal values for the copper, iron and hemoglobin contents of the blood from birth to the adult stage It bridges the gap existing in normal figures obtained in this series of studies for persons between 15 years of age and adult ages² This period may be designated as late adolescence or possibly as the preadult stage, and in the present study these terms will be used arbitrarily to refer to the interval between the ages of 14 and 19 years

This age period is of special interest because it is during this time that the sex differentiation which is apparent in the blood iron values for adults but absent in those for children makes its appearance This

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1 Sachs, A , Levine, V E, and Fabian, A A Copper and Iron in Human Blood I Normal Men and Women, Arch Int Med **55** 227 (Feb) 1935

2 Sachs, A , Levine, V E, and Fabian, A A Copper and Iron in Human Blood IV Normal Children, Arch Int Med **58** 523 (Sept) 1936

period is likewise of interest in establishing the age at which the values for adults are reached and whether males and females attain these values at the same age

METHODS

The determinations of iron and copper reported in this paper were made during the period from November 1935 to May 1936

The normal adolescent boys were from Father Flanagan's Boys' Home, at Boystown, Neb. The normal adolescent girls were from South High School, in

TABLE 1—*Values for Copper and Iron in Blood of Normal Adolescent Boys*

Name	Age, Years	Red Blood Cells per Cu Mm	Copper, Mg per 100 Cc	Iron, Mg per 100 Cc (Wong)	Iron, Mg per 100 Cc (Ash)	Hemo- globin, Gm per 100 Cc *	Hemo- globin, %†	Iron Color Index‡
W H	14	5,180,000	0.1688	49.82	49.60	14.81	98	0.95
C O	14	4,544,000	0.1446	50.26	50.32	15.02	93	1.11
W H	14	4,416,000	0.1720	41.64	40.80	11.88	90	0.93
F S	14	5,056,000	0.1550	45.06	44.12	13.17	97	0.86
B O	14	4,800,000	0.1656	48.40	48.40	14.45	93	1.00
T M	15	5,184,000	0.1722	46.46	45.72	13.65	94	0.88
J H	15	4,672,000	0.1566	45.84	45.96	13.72	92	0.98
M T	15	5,056,000	0.1782	46.96	46.80	13.97	93	0.92
B U	15	5,568,000	0.1594	48.20	46.90	14.00	99	0.84
F L	16	4,832,000	0.1556	45.04	44.20	13.19	96	0.92
B R	16	5,088,000	0.1566	46.50	46.24	13.80	93	0.90
S R	16	4,896,000	0.1686	40.46	39.60	11.82	94	0.82
N E	16	4,704,000	0.1526	46.42	45.96	13.79	98	0.98
O T	16	4,416,000	0.1598	45.90	46.80	13.97	88	1.07
H N	16½	4,992,000	0.1494	51.00	51.28	15.31	98	1.02
K Y	17	5,440,000	0.1482	50.50	50.00	14.92	101	0.93
H Y	17	4,992,000	0.1548	50.86	51.60	15.40	97	1.04
H G	17	5,024,000	0.1580	48.36	48.60	14.51	98	0.97
C U	17	5,128,000	0.1270	52.42	53.12	15.85	101	1.04
L N	18	5,024,000	0.1432	51.00	50.64	15.11	92	1.01
B C	18	4,672,000	0.1394	50.20	50.96	15.21	93	1.08
N E	18	4,992,000	0.1364	50.75	51.62	15.41	100	1.03
McG	19	4,640,000	0.1314	49.90	50.64	15.11	94	1.09
Average		4,927,000	0.1545	47.91	47.82	14.26	95	0.97

* Hemoglobin values were determined from the iron content of the blood obtained by the use of the Butterfield factor—iron equals 0.335 per cent of the hemoglobin molecule (Butterfield, E. Ztschr f physiol Chem **62** 173, 1909)

† The percentages of hemoglobin were determined with the Dare hemoglobinometer

‡ The iron color index ¹ equals $\frac{\text{Mg of iron in 100 cc of blood}}{\text{First two figures of red cell count}}$

Omaha. All were in a good state of health, and the red cell, white cell and differential white cell counts were within normal limits. For all the girls who had reached the age of development characterized by the onset of the menstrual cycle, the sample of blood was drawn in every case in the intermenstrual period to eliminate any possible altering effect of this physiologic process on the blood iron or copper. One investigator, Sarata,³ has claimed that the copper value varies greatly with the menstrual phases. Work done in this laboratory

3 Sarata, U. Studies in Biochemistry of Copper. VI Copper in Relation to Menstruation and Pregnancy, Jap J M Sc, II, Biochem **3** 1 (Feb) 1935

that is soon to be published indicates that in the subjects studied there was no evident relation between the copper content of the blood and the menstrual cycle except when the flow was excessive and the loss of iron was marked

Blood counts were made with standardized pipets and counting chambers for blood drawn from the lobe of the ear

Samples of venous blood were taken from the basilic vein, platinum needles being used. The syringes were rinsed in water free from iron and copper, wrapped in towels and sterilized in an autoclave

TABLE 2—*Values for Copper and Iron in Blood of Normal Adolescent Girls**

Name	Age, Years	Red Blood Cells per Cu Mm	Copper, Mg per 100 Cc	Iron, Mg per 100 Cc (Wong)	Iron, Mg per 100 Cc (Ash)	Hemo globin, Gm per 100 Cc	Hemo globin, %	Iron Color Index
K O	14	5,056,000	0.1582	43.42	44.24	13.21	97	0.87
D A	14	4,576,000	0.1360	46.60	47.04	14.04	94	1.02
W L	14	4,704,000	0.1348	46.26	46.94	14.01	93	0.99
B R	14	4,096,000	0.1320	42.90	43.00	12.84	87	1.05
R C	14	4,320,000	0.1460	45.32	45.20	13.49	89	1.05
D A	15	4,320,000	0.1380	44.10	45.20	13.49	88	1.05
M C	15	4,864,000	0.1334	45.94	46.24	13.80	91	0.95
P O	15	4,672,000	0.1430	44.20	44.20	13.19	91	0.95
H N	15	5,120,000	0.1194	47.10	47.48	14.17	99	0.92
W S	15	4,928,000	0.1264	49.82	50.32	15.04	97	1.02
K O	15	4,704,000	0.1400	47.04	47.96	14.31	98	1.02
W L	16	4,736,000	0.1350	41.60	42.32	12.63	90	0.89
D V	16	4,864,000	0.1564	46.86	46.60	13.91	93	0.96
K A	16	4,544,000	0.1302	46.24	46.24	13.80	93	1.02
B U	16	4,352,000	0.1354	47.80	48.28	14.41	86	1.11
S I	16	4,608,000	0.1336	42.40	43.24	12.91	84	0.93
H R	16	4,864,000	0.1502	48.80	49.68	14.83	92	1.02
B L	16	4,096,000	0.1442	42.12	42.12	12.57	87	1.02
V L	16	3,936,000	0.1436	44.42	44.68	13.34	83	1.13
L N	16	4,352,000	0.1180	45.16	45.20	13.49	95	1.04
K L	17	4,576,000	0.1582	43.20	43.48	12.98	86	0.95
H L	17	4,800,000	0.1350	46.96	47.20	14.09	96	0.98
F L	17	4,192,000	0.1370	44.98	46.80	13.97	93	1.12
McG	17	4,736,000	0.1332	43.00	42.32	12.63	90	0.89
W I	18	4,672,000	0.1302	41.86	42.76	12.76	86	0.91
O A	18	5,216,000	0.1352	46.72	46.94	14.01	100	0.90
O B	18	4,640,000	0.1442	46.46	47.22	14.09	93	1.02
O B	18	4,544,000	0.1482	42.40	42.56	12.70	89	0.93
O R	18	4,864,000	0.1486	46.22	46.52	13.89	90	0.96
Average		4,622,000	0.1387	45.17	45.58	13.61	91	0.99

* See footnotes for table 1

Special precautions were taken to obtain pure reagents, free from copper and iron. Acids, alkalis and water were redistilled from glass and were tested at frequent intervals for contamination.

The procedure used for the determination of copper was an iron precipitation modification of the method devised by McFarlane,⁴ the reagent used being sodium diethyldithiocarbamate, described by Callan and Henderson.⁵

4 McFarlane, W. D. Application of the Sodium Diethyldithiocarbamate Reaction to the Micro-Colorimetric Determination of Copper in Organic Substances, *Biochem J* **26** 1022, 1932

5 Callan, T., and Henderson, J. A. R. New Reagent for Colorimetric Determination of Minute Amounts of Copper, *Analyst* **54** 650 (Nov) 1929

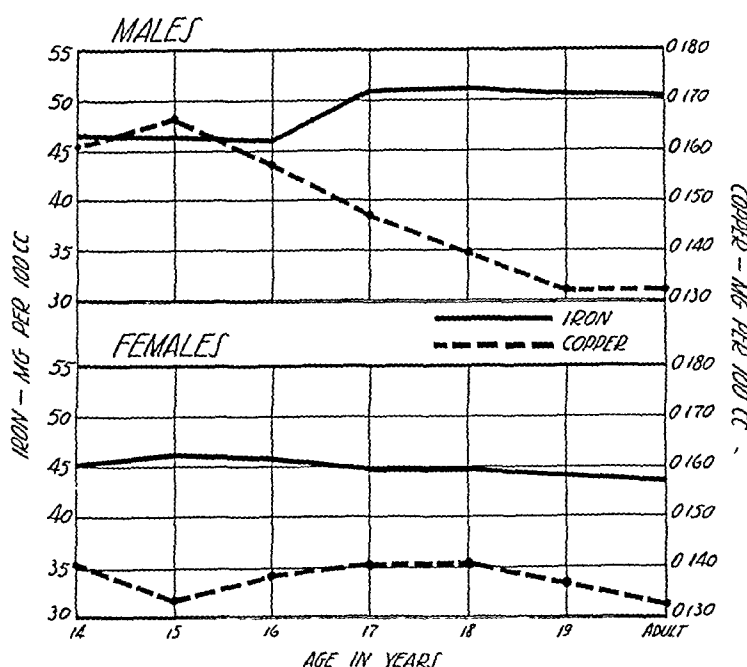


Chart 1—Curves showing copper and iron values for boys and girls between the ages of 14 and 19 years. The normal averages for adults are included for comparison.

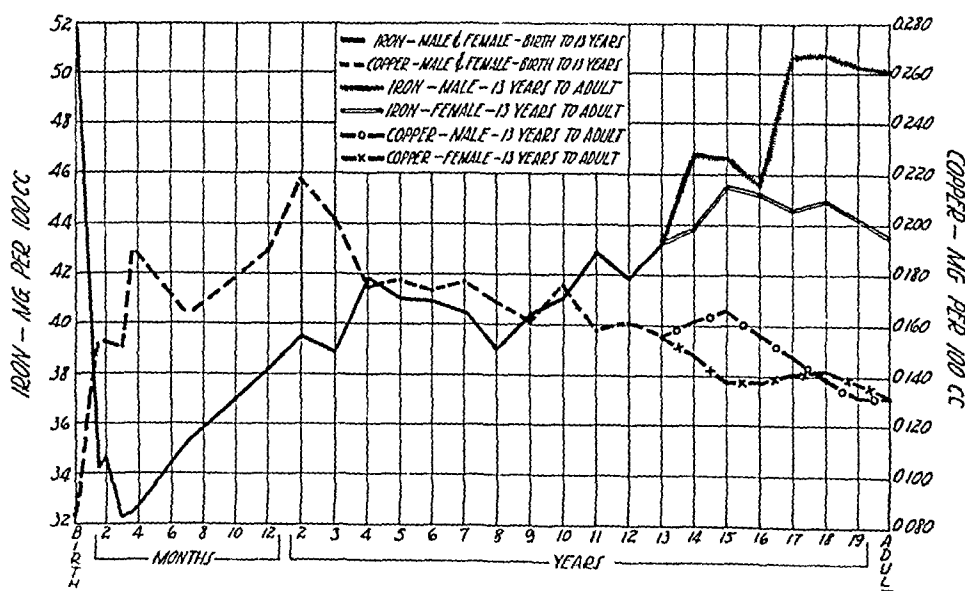


Chart 2—Curves showing copper and iron values for males and females from birth to the adult state. These averages include all figures reported in this and in previous papers in this series^{1, 2}.

For the determinations of the iron content two methods were used which served as a check one on the other

Details of the method for determining the copper values¹ as well as the two methods for determining the iron values⁶ have previously been described

TABLE 3—*Averages of Blood Values for Fifty-Two Normal Boys and Girls Listed in Tables 1 and 2*

Boys	Average	Ranges
Copper, mg per 100 cc	0.1545 \pm 0.0088*	0.131-0.178
Iron, mg per 100 cc (both methods)	47.865 \pm 2.165	39.60-53.12
Hemoglobin, Gm per 100 cc	14.26 \pm 0.608	11.82-15.85
Red cells per cu mm	4,927,000	4,416,000-5,568,000
Iron color index	0.97	0.82-1.11
Girls		
Copper, mg per 100 cc	0.1387 \pm 0.0067	0.118-0.158
Iron, mg per 100 cc (both methods)	45.375 \pm 1.44	41.60-50.32
Hemoglobin, Gm per 100 cc	13.61 \pm 0.412	12.57-15.04
Red cells per cu mm	4,622,000	3,936,000-5,216,000
Iron color index	0.99	0.87-1.13

* This is the probable error of distribution. Thus, there is a fifty-fifty chance that the copper content of normal whole blood for this age period will fall somewhere within the range between average plus probable error and average minus probable error.

TABLE 4—*Average Values for Copper, Iron and Hemoglobin in Blood of Normal Adolescent Boys and Girls*

	Age, Years	Red Blood Cells per Cu Mm	Copper, Mg per 100 Cc	Iron, Mg per 100 Cc (Wong)	Iron, Mg per 100 Cc (Ash)	Hemoglobin, Gm per 100 Cc
Boys	14	4,799,000	0.1612	47.04	46.65	13.87
	15	5,120,000	0.1666	46.87	46.35	13.84
	16	4,821,000	0.1571	45.89	45.68	13.65
	17	5,146,000	0.1470	50.54	50.83	15.17
	18	4,896,000	0.1397	50.65	51.07	15.24
	19	4,640,000	0.1314	49.90	50.64	15.11
Girls	14	4,550,000	0.1412	44.90	45.28	13.52
	15	4,768,000	0.1334	46.37	46.90	14.00
	16	4,484,000	0.1385	45.04	45.48	13.54
	17	4,576,000	0.1408	44.54	44.95	13.42
	18	4,787,000	0.1413	44.73	45.20	13.49

In every case the sample of blood was drawn in a preabsorptive period, at noon, just before lunch. The time is specified because Rabinowitch⁷ has shown that the hemoglobin content varies somewhat at different periods of the day.

6 Fabian, A. A., Sachs, A., and Levine, V. E. Comparison of Wet and Dry Ashing Methods for Determining Blood Iron, *Proc. Soc. Exper. Biol. & Med.* **32**: 662 (Jan.) 1935.

7 Rabinowitch, I. M. Variations of the Percentage of Hemoglobin in Man During the Day, *J. Lab. & Clin. Med.* **9**: 120, 1923.

COMMENT

The period of adolescence is one of instability and adjustment. It is the period of transition from childhood to the adult state, and it is marked by many important physiologic changes. The blood picture based on the iron, hemoglobin and copper contents for boys and girls ranging in age from 14 to 19 years likewise shows a transition from childhood to the adult state. These data exhibit some variation among children within the same yearly age groups, but the averages point to some definite trends.

It was noted in the paper on normal children² that up to the fourteenth year of life there was little or no difference in the copper and iron values for boys and girls of any given age. In the preadult group reported on in the present paper, however, a definite differentiation is seen which is based on sex as well as on age. It appears that between the fourteenth and the sixteenth year of life the values for iron are only slightly higher for boys than for girls. Between the ages of 16 and 17 years, however, the iron picture for boys changes rapidly from 45 mg per hundred cubic centimeters to the men's average of 50 mg per hundred cubic centimeters. The figure for girls, on the other hand, at 14 years equals the mode for iron of women, which is 45 mg per hundred cubic centimeters and remains rather constant at that average.

The red cell counts reflected in a curve do not exactly parallel the iron and hemoglobin values, but they are consistently higher for boys.

The figures for copper compared with those for adults are seen to be higher in children². These diminish during the adolescent period until those for boys reach the level for men at about 18 years of age. In girls the copper level for women is reached at about the fourteenth or fifteenth year of life. This average copper value for adults, which is the same for men and women, has previously been established at 0.132 mg per hundred cubic centimeters of blood.¹

It seems, on the basis of the iron and copper values, that girls reach maturity at a younger age than boys. The results of this investigation establish maturity in girls at 14 or 15 years and in boys at 17 or 18 years of age. Grigorowa⁸ has shown that girls begin to show signs of maturity from two to three years earlier than do boys, basing the stages of development on physical signs, such as the development of the breasts, pubic and axillary hair and changes in the voice. Topper and Mulier,⁹ in a study of the basal metabolism of normal boys and girls, have shown a definite increase in metabolism in early puberty followed

8 Grigorowa, O. Blood Picture During the Pubertal Period, *Ztschr f d ges Anat (Abt 2)* **15** 24 (Nov 26) 1929

9 Topper, A., and Mulier, H. Basal Metabolism of Normal Children The Puberty Reaction, *Am J Dis Child* **43** 327 (Feb) 1932

by a fall after puberty has been established. The rise was found to occur from one to two years earlier in girls than in boys. They stated that "this increase coincides with the physiologic age rather than with the chronological age, and occurs earlier in girls than in boys, coincident with their earlier pubescence." Holt and Howland¹⁰ have cited figures to show that boys and girls grow at approximately the same rate up to the time of puberty, the girls pass the boys during the twelfth and thirteenth years, but the boys then pass the girls at the fourteenth and fifteenth years.

Several investigations of hemoglobin and red cell contents of the blood of adolescent children are reported in the literature. Borchers¹¹ has stated that in boys the red blood cell and hemoglobin values for adults are attained at 18 years of age. Williamson,¹² after a large series of determinations, made by a spectrophotometric method, has reported that hemoglobin values from birth to the fifteenth year are almost identical for the two sexes. From the sixteenth year on, however, he found that hemoglobin values are considerably lower for females. This agrees well with the findings in the present study as well as with those in the previous report in this series on normal children,² although Williamson's values are higher. According to Osgood,¹³ however, Williamson's figures are generally recognized as being too high, and he has advocated deducting 10 per cent from them. If this is done they agree well with the hemoglobin values based on iron determinations obtained in the present study. Osgood¹³ established normal hematologic standards for a large series, reporting red cell counts, hemoglobin values, color indexes, cell volumes, volume and saturation indexes, reticulocyte counts, leukocyte and differential counts and sedimentation rates. He has reported that the concentration of hemoglobin increases at the same rate for the two sexes until the age of 14, when the values for boys increase more rapidly, quickly reaching the values for adults. This more rapid increase in the hemoglobin value in the boys reported on in his charts shows trends similar to those observed in the present study.

One or two investigators have observed that children from orphanages and institutions show lower figures for hemoglobin than those of

10 Holt, L. E., and Howland, John. *Holt's Diseases of Infancy and Childhood*, ed 10, revised by L. E. Holt Jr., and R. McIntosh, New York, D. Appleton-Century Company, Inc., 1936, pp 21-22.

11 Borchers, J. *Das rote Blutbild gesunder jugendlicher männlichen Geschlechtes im Alter von 13 bis 20 Jahren*, *Folia haemat* **54** 387, 1936.

12 Williamson, C. S. *Influence of Age and Sex on Hemoglobin. A Spectrophotometric Analysis of Nine Hundred and Nineteen Cases*, *Arch Int Med* **18** 505 (Oct) 1916.

13 Osgood, E. E. *Normal Hematologic Standards*, *Arch Int Med* **56** 849 (Nov) 1935.

similar age from private homes or families. This is a valid objection to the study of children from institutions where the health and food requirements are neglected through mismanagement. However, the boys included in this study were all in a good state of health, and the institution from which they came was well managed and free from political influence. Furthermore, Osgood¹³ has stated that results for persons of different social classes used in his study, including children from grade schools, orphan asylums, homes for infants and physicians' families, showed no significant differences.

SUMMARY

Values for the copper, iron, hemoglobin and red cells of the blood were determined for a series of normal boys and girls ranging in age from 14 to 19 years.

The average copper content of whole blood was found to be 0.1545 ± 0.0088 mg per hundred cubic centimeters for boys and 0.1387 ± 0.0067 mg for girls.

The average iron content of whole blood was found to be 47.865 ± 2.165 mg per hundred cubic centimeters for boys and 45.375 ± 1.440 mg for girls.

The average hemoglobin content of the blood was 14.26 ± 0.608 Gm per hundred cubic centimeters for boys and 13.61 ± 0.412 Gm for girls.

The average red cell count was 4,927,000 per cubic millimeter for boys and 4,622,000 for girls.

In an earlier study of children it was noted that the iron and hemoglobin values gradually increased after 3 months of age up to the age of 14 years. The averages were the same for boys as for girls.² The present study shows that by the fourteenth year of life the values for both sexes are equivalent to the average value for women. In girls after the fourteenth year the values for iron and hemoglobin become rather constant. The figures for boys, on the other hand, increase only slightly between the ages of 14 and 16 but rise sharply after the sixteenth year, to reach the average value for men by the seventeenth year. It seems, therefore, that differences in the values for iron and hemoglobin due to sex become apparent after the age of 16 years.

The iron and copper values for women were reached by the girls by the fourteenth or fifteenth year, whereas the boys did not attain the values for men until the seventeenth or eighteenth year. This is in accord with other evidences of earlier maturity in girls.

Mr W. A. Dwyer, of the Department of Mathematics, Creighton University, made the statistical analysis of our data.

SYMPATHECTOMY FOR PERIPHERAL VASCULAR DISEASE

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A number of arguments have been brought forward against the use of sympathectomy in the treatment of peripheral circulatory disturbances. The purpose of this communication is to examine the validity of these objections in the light of personal experience. Fifty patients have been subjected in my clinic to one hundred and twenty-six sympathectomies (table 1). However, the data for only twenty-four

TABLE 1—*Indications for Sympathectomy in Peripheral Circulatory Disturbances*

Diagnosis	Total Number of Patients	Number of Patients Operated On*	Indications
Raynaud's phenomena	25	6 (15)	Lack of marked structural changes in the vessels, absence of sclerodactylia
Buerger's disease	125	10 (21)	Definite collateral reserve, absence of acute inflammation or arteriolar destruction, poor response to conservative treatment
Poliomyelitis	25	3 (9)	Moderate paralysis limited to one extremity, evidence of vasospastic phenomena, age preferably between 6 and 10 years
Reflex dystrophy (causalgia, traumatic vessel spasm and Sudeck's atrophy)	5	5 (5)	Severe involvement, resistance to physical therapy, exaggerated vasomotor responses
	180	24 (50)	

* The figures in parentheses indicate the number of patients operated on up to Sept. 1, 1936. For a study of the end results only those patients have been included who have gone through one or two winters' study of the group recently operated on, however, has helped to clarify indications and technique.

of these patients, with forty-six sympathectomies, have been used for the evaluation of results, as these patients have been followed for one year or more since operation, the longest period of observation being seven years. Study of the patients more recently operated on has served only to clarify the indications and lead to modifications of the technical procedures.

In the main, four arguments are brought forward against sympathectomy. 1. The peripheral circulation, although temporarily modified after the operation, returns to a preoperative level within from sixteen to twenty-one days. 2. Permanent sympathetic denervation of

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an extremity is impossible, as the fibers will regenerate and restore continuity with the vessels. 3 The diseases for which the operation is undertaken are not diseases of the vasomotor system. 4 The clinical benefit derived from these operations is often slight and sometimes negligible.

1 RETURN OF THE PERIPHERAL CIRCULATION TO THE PREOPERATIVE LEVEL

The first argument, namely, that the peripheral circulation returns in a short time to the preoperative level, has been maintained by Johnson and his co-workers.¹ They showed in careful studies on several sympathectomized patients that the pulse volume of the fingers, as measured with Johnson's plethysmograph, returns to the preoperative level in a short time. They also found evidence that the vessels react to direct application of heat by vasodilatation. These findings are important, as they show that, just as in the experimental animal, vascular tonus, or the tonus of the smooth muscle of the vessels, is regained after a short initial period of vasodilatation. While this phenomenon was registered as early as 1874 by Goltz and Freusberg for the experimental animal,² it was felt for a while that in man a permanent loss of vascular tonus results after sympathectomy.

The observations which my colleagues and I have made indicate, however, that in spite of a recovery of vascular tonus, the peripheral circulation is far from what it was before sympathectomy. The vessels do react to direct application of heat and cold (fig 1) and they also react to the metabolic requirement of the tissues, because reactive hyperemia can be readily produced after arterial occlusion in the sympathectomized or in the completely denervated extremity. But, being deprived of vasomotor influences, these vessels are freed of a number of important extrinsic and intrinsic stimuli which come continuously or intermittently over the efferent sympathetic pathways. Thus cooling or pinching the body, pain, fright or anger cannot produce vasoconstriction in the sympathectomized extremity³ (fig 2), nor will heating the body⁴ or the production of fever with typhoid vaccine^{1a} produce

1 (a) Johnson, C. A., Scupham, G. W., and Gilbert, N. C. Studies on Peripheral Vascular Phenomena. II. Observations on Peripheral Circulatory Changes Following Unilateral Cervical Ganglionectomy and Ramisectomy, *Surg., Gynec. & Obst.* **55** 737, 1932. (b) Johnson, C. A., and Davis, Loyal. Paper presented at the meeting of the Central Society for Clinical Research, Chicago, Nov. 7, 1936.

2 Goltz, F., and Freusberg, A. Ueber gefässerweiternde Nerven, *Arch. f. d. ges. Physiol.* **9** 174, 1874.

3 Sturup, G., Bolton, B., Williams, D. J., and Carmichael, E. A. Vasomotor Responses in Hemiplegic Patients, *Brain* **58** 456, 1935.

4 Lewis, T., and Landis, E. M. Some Physiological Effects of Sympathetic Ganglionectomy in the Human Being and Its Effect in a Case of Raynaud's Malady, *Heart* **15** 151, 1930.

vasodilatation The normal vascular tree is in constant motion, regulating temperature and blood pressure, but it can be easily shown that the diseased vascular tree is more seriously affected by these vasomotor impulses because it is narrower or more sensitive A study of the course of peripheral vascular disease reveals that nothing benefits the patient more than rest in bed and continuous mild heat A draft or a chill or an emotional upset readily reflects itself on the state of the peripheral circulation Sympathectomy for these diseased and inflamed vessels means rest from central or reflex stimuli, which to my mind plays an important rôle in regulating blood supply

It must also be emphasized that a diseased vessel, such as a thrombosed artery in Buerger's disease, in itself is responsible for maintaining spasm of the collateral vessels In an article entitled "Reflex Dystrophy of the Extremities" I⁵ have traced this spinal reflex as going through a sensory pathway to the spinal cord and emerging as a sympathetic efferent stimulus through the anterior roots (fig 3) Sometimes it is

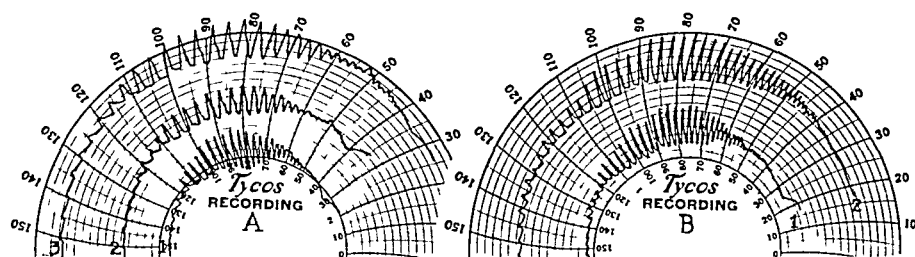


Fig 1—The effect of cold, heat and arterial occlusion on the vascular bed of the sympathectomized limb A, Mrs E V, aged 27 years, had been suffering from Raynaud's disease Preganglionic sympathectomy had been performed on the left side five days previously 1 shows the control curve, 2, the curve after five minutes in water at 15 C and 3, the curve after five minutes in water at 40 C Note the vasoconstriction due to cold and the vasodilatation due to heat B, 1, control curve and, 2, after two minutes of constriction with 200 mm of mercury during the first minute of release Each spike denotes the change of volume with each beat The height of the spikes and the shift of the oscillographic curve to the right indicate the state of peripheral resistance These charts illustrate that even as early as five days after sympathectomy the circulation is controlled by direct response to the environmental temperature The reactive hyperemia after arterial occlusion is marked and indicates that metabolic products accumulating during ischemia can produce a further increase in blood flow even during the immediate "maximal" vasodilatation which occurs in the first few days after sympathectomy

possible to interrupt the afferent side of the reflex by excising the focus of irritation Thus, in one patient the excision of a thrombosed axillary vein and in another the stripping of an iliac vein due to old lymphangitis and periphlebitis promptly relieved the vasomotor and trophic phe-

5 de Takats, G Reflex Dystrophy of the Extremities, Arch Surg **34** 939 (May) 1937

nomena When these exaggerated vasomotor and nutritional reflexes are allowed to persist for a certain length of time, definite nutritional disturbances, such as osteoporosis, muscular atrophy, stiffness of joints and sclerosis of connective tissue, develop and are not always reversible

In most patients suffering from peripheral vascular disease local segmental excision of the irritating focus is impossible This procedure has been advocated by Leriche,⁶ but massive arterial resections can seldom be complete Recently Clute⁷ performed excision for localized arteritis, with striking improvement in circulation In the majority of cases the interruption of the afferent arc will not be feasible Sympa-

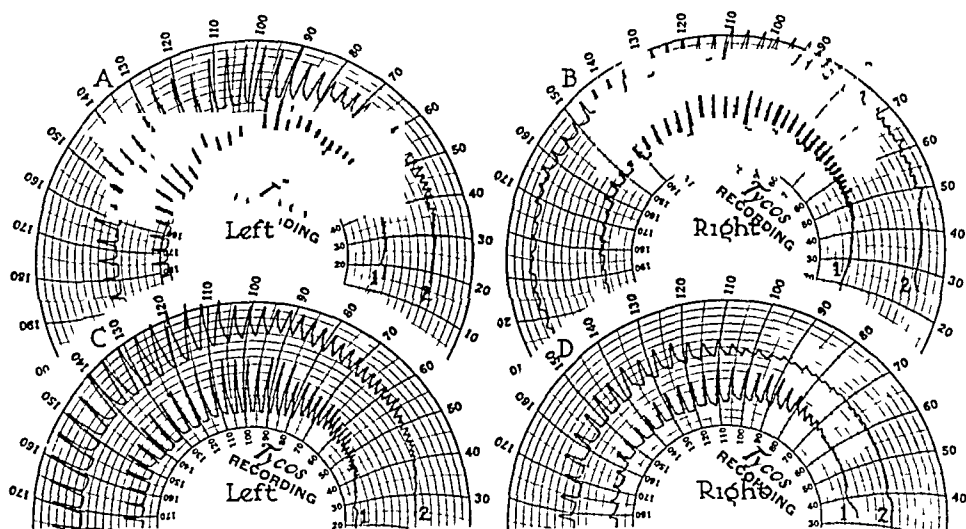


Fig 2—The effect of pain and cold on the circulation of the sympathectomized limb in H M, a 29 year old woman suffering from a reflex dystrophy following mild trauma to the left foot Left lumbar sympathectomy had been performed two months previously Graphs A and B show the effect of pain on the circulation of the left sympathectomized limb as compared with that on the circulation of the right control limb Pain was induced by injecting 0.4 cc of 1:1,000 solution of histamine intradermally While there is no appreciable difference in the sympathectomized limb after the painful stimulus, there is a definite vasoconstriction in the control limb Note especially the diminution in the height of the spikes at 80 mm of mercury In graphs C and D the combined effect of cold, surprise and anger are demonstrated in the same patient Both hands were immersed in ice-water for one minute, after the oscillogram was started an ether spray was directed against the area behind the ears, taking the patient by surprise This combination of stimuli produced slight vasoconstriction in the sympathectomized limb, owing perhaps to an epinephrine effect, but the control side showed a marked increase in peripheral resistance The pulse waves became small at 100 mm of mercury, whereas the control showed similar oscillations at 70 mm of mercury

6 Leriche, R, and Fontaine, R Conditions necessaires, resultats et technique de l'arteriectomie, Presse med **43** 1953 (Dec 4) 1935

7 Clute, H M Acute Arterial Obstruction from Arteritis, New England J Med **214** 137 (Jan 23) 1936

thectomy interrupts the efferent arc, and the beneficial results in Buerger's disease and in reflex dystrophies, such as traumatic osteoporosis, Sudeck's atrophy, causalgia and stump neuroma, are at least partly due to the interruption of this spinal reflex

On the basis of these findings one must admit the beneficial effect of permanent vasomotor palsy on the impaired peripheral circulation. In addition, Hick and I⁸ have recently reported another finding which points to an improvement in circulation after sympathectomy. The oxygen saturation of the venous blood, taken from the femoral or

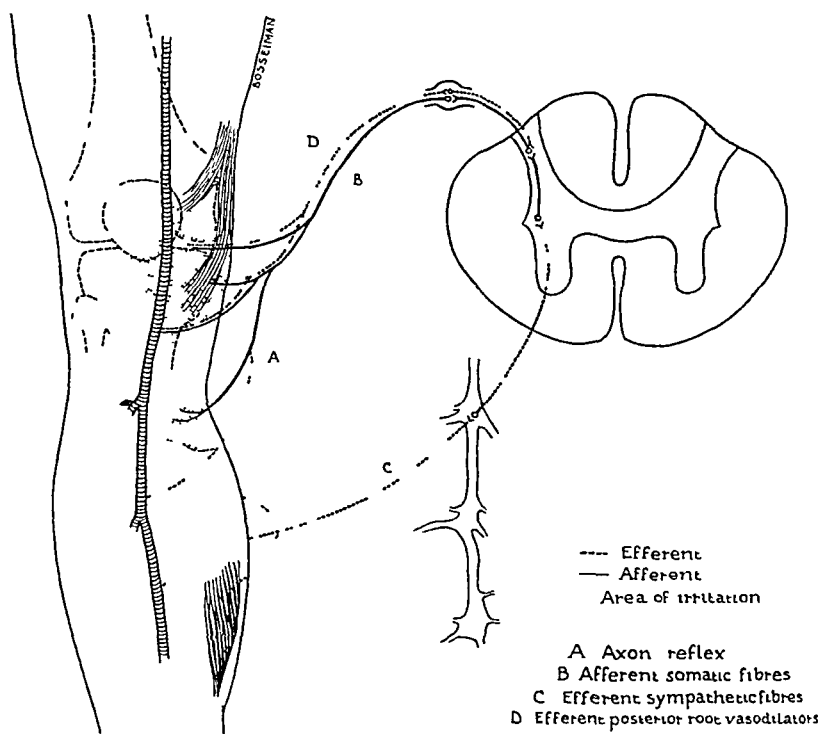


Fig 3—The pathway of a spinal sensory-sympathetic reflex operating in certain vasomotor and nutritional disturbances. This reflex is responsible for shutting down the collateral vessels in acute arterial occlusion (de Takats, G. Acute Arterial Occlusions of Extremities, *Am J Surg* **33** 60 [July] 1936), but it also operates in the posttraumatic reflex dystrophies as a result of a slow continuous stimulus, producing vasodilatation, edema and osteoporosis⁵

cubital vein, rises after the operation (table 2). The rise does not occur if patients with advanced involvement and with no capacity for collateral reserve are subjected to operation. The rise is marked if there are only slight organic changes or none at all in the vessels, as in cases of early Raynaud's disease or reflex dystrophy. This finding

⁸ Hick, F. K., and de Takáts, G. The Value of Sympathectomy in the Treatment of Peripheral Vascular Disease, to be published

is direct evidence that the supply of oxygen to the tissues is increased after sympathectomy, because the venous-oxygen content reflects the oxygen tension in the tissues, provided arterial oxygen saturation is normal. When the venous oxygen saturation does not rise, the clinical results are poor. The vascular bed in these patients is fixed and is not capable of dilatation. The detection and elimination of these patients by preoperative tests will be discussed later.

2 REGENERATION OF SYMPATHETIC FIBERS

The second important argument against sympathectomy is the regeneration of sympathetic fibers and the restoration of their functional

TABLE 2—*The Effect of Sympathectomy on Venous Oxygen Content and Saturation* *

Case No	Initials	Diagnosis	Side	Before Operation			Two Weeks After Operation			Several Months After Operation		
				Oxy- gen Con- tent, Vol %	Oxy- gen Satu- ration, Vol %	Oxy- gen Capac- ity, Vol %	Oxy- gen Con- tent, Vol %	Oxy- gen Satu- ration, Vol %	Oxy- gen Capac- ity, Vol %	Oxy- gen Con- tent, Vol %	Oxy- gen Satu- ration, Vol %	Oxy- gen Capac- ity, Vol %
1	S L	Buerger's disease	L	11.75	61.4		8.46	45.8		9.02	48.4	
			R	6.93	36.3		8.85	47.5		9.53	50.9	
						19.10			18.46			18.70
2	F N	Buerger's disease	L	11.63	62.9		12.68	77.4		11.90	79.0	
			R							6.62	44.0	
						18.48			16.36			15.05
3	J G	Buerger's disease Arms	L	16.00	83.7					15.90	90.8	
			R	14.90	77.4					15.20	85.7	
			L				10.92	62.4				
			R				12.66	72.4				
4	A J	Raynaud's disease Arms	L	7.87	42.5		15.86	83.0		10.92	60.4	
			R				13.60	73.6		12.74	70.4	
		Legs	L	9.88	46.7					8.52	58.4†	
			R	7.92	58.4					11.05	76.2	
						16.93			19.10			18.06

* In patients who show poor clinical results the oxygen saturation does not rise after sympathectomy (in case 1, both lower extremities, in case 2, the right lower extremity). In patients who still show a capacity for vasodilatation and in whom favorable results have been obtained, the oxygen saturation rises and remains high after sympathectomy.

† On the side not operated on.

activity. In 1935 Cuthbert and I,⁹ studying the effect of section of the splanchnic nerve on the sugar tolerance of dogs, stated that regeneration of the splanchnic nerves can hardly be prevented unless the proximal stump is implanted into a peripheral nerve. This was carried out on diabetic children on whom section of the splanchnic nerve had been per-

⁹ de Takáts, G., and Cuthbert, F. P. Effect of Suprarenal Denervation and Splanchnic Section on the Sugar Tolerance of Dogs, *Arch Surg* **30** 151 (Jan) 1935.

formed¹⁰ Simple section of the trunk of the thoracic sympathetic chain, as practiced by Royle,¹¹ is likely to be followed by regeneration, although no histologic proof in man has ever been presented. The complete removal of the ganglionated trunk with its postganglionic fibers can show evidence of regeneration only if (1) the operation did not remove all the excitator ganglions and if some postganglionic fibers escaped section or (2) if a preganglionic section of the trunk was carried out, after which the preganglionic fibers readily established connections with the intact ganglions and their postganglionic fibers. A third possibility is that the two-neuron theory of Langley—that the sympathetic nervous system consists of a massive syncytical network of fibers and ganglions—is incorrect. Not only are the ganglions present in the cord and in the sympathetic ganglions, but they are scattered in the periphery and are capable of regenerating fibers, of automatic function and of reflex activity. This theory has been advanced by Stohr,¹² and should it be correct, regeneration of fibers and return of function could be explained even if complete, so-called preganglionic and postganglionic section had taken place. Restoration of peripheral resistance in completely sympathectomized animals has recently been reported by Wilson, Roome and Grimson,¹³ from Phemister's department at the University of Chicago.

Should Stohr's theory be correct and if regeneration and automatic activity of these peripheral ganglions and terminal network occurred after their severance from the cord, I still believe that permanent benefit is derived from sympathectomy. The lower centers, while active, will be uninhibited by higher nervous activity. Central and reflex stimuli do not reach them. They are stimulated by metabolic activities of the tissues and by thermal influences. So again one must come to the conclusion that the blood flow is more even and less inhibited than before operation. Only if the regeneration of the sympathetic fibers could reestablish normal connections with the cord would a preoperative state be reached.

However, until more evidence accumulates, the theory of Langley still stands, and there is ample histologic evidence to show that transection of preganglionic fibers leaves the terminal ganglion and post-

10 de Takats, G. Splanchnic Nerve Section in Juvenile Diabetes. II. Technique and Postoperative Management, *Ann Surg* **102** 22 (July) 1935.

11 Royle, N. D. Sympathetic Trunk Section. A New Operation for Raynaud's Disease and Spastic Paralysis of the Upper Limb, *M. J. Australia* **2** 436 (Oct. 6) 1928.

12 Stohr, P., Jr. Bemerkungen zur Gefässinnervation, *Zentralbl. f. Chir.* **61** 2 (Jan. 6) 1934.

13 Wilson, H., Roome, N. W., and Grimson, K. Complete Sympathectomy. Observations on Certain Vascular Reactions During and After Complete Exclusion of the Sympathetic Nervous System of Dogs. *Ann Surg* **103** 498 1936.

ganglionic fiber intact, whereas removal of the ganglion produces postganglionic degeneration but leaves the upper neuron intact¹⁴

The regaining of vascular tonus has been interpreted recently as an increased sensitivity to hormones, such as epinephrine,¹⁵ when the postganglionic fiber degenerates¹⁶ Therefore, following the advice of Smithwick, Freeman and White and Telford,¹⁷ efforts have been made to restrict sympathectomy to preganglionic sections My colleagues and I have had favorable experience with these operations All lumbar sympathectomies are predominantly preganglionic sections, as the ganglions for the lower extremity are mostly in the lowest lumbar and upper sacral ganglions In the upper extremity, however, the usual excision of the inferior cervical and first and second thoracic ganglions removes the excitator ganglions, and postganglionic degeneration occurs To overcome this, Smithwick¹⁸ has recently described preganglionic section for the upper extremity by sectioning the dorsal sympathetic chain below the third ganglion and removing the proximal inch (2.5 cm) of the second and third intercostal nerves More recently he has extended this operation so that the dissection of the intercostal nerves is carried into the intervertebral foramen and includes dividing the dural attachments and sectioning the anterior and posterior roots as well In my clinic the Smithwick operation has been carried out only twice, whereas another approach from the front, as suggested by Telford, has been used sixteen times Time will show the per-

14 Ransom, S W The Anatomy of the Autonomic Nervous System with Special Reference to the Innervation of Skeletal Muscles and Blood Vessels, *Ann Int Med* **6** 1013, 1933 Lawrentjew, B I Weitere Untersuchungen über die Degeneration und Regeneration von Synapsen, *Ztschr f mikr-anat Forsch* **35** 71, 1934 Lawrentjew, B I, and Boroskaja, A J Die Degeneration der postganglionaren Fasern des autonomen Nervensystems und deren Endigungen, *Ztschr f Zellforsch u mikr Anat* **23** 761, 1936

15 Freeman, N E, Smithwick, R H, and White, J C Reactions of the Blood Vessels of the Human Extremity, Sensitized by Sympathectomy to Adrenaline and to Adrenal Secretion Resulting from Insulin Hypoglycemia, *Am J Physiol* **107** 529, 1934

16 As reported in a joint communication with Sanford Gifford (Cervical Sympathectomy in Retinitis Pigmentosa, *Arch Ophth* **14** 441 [Sept] 1935), the difference of preganglionic and postganglionic sections on the effect of pupillary reactions to epinephrine can easily be demonstrated

17 Smithwick, R H, Freeman, N E, and White, J C The Effect of Epinephrine on the Sympathectomized Human Extremity An Additional Cause of Failure of Operations for Raynaud's Disease, *Arch Surg* **29** 759 (Nov) 1934 White, J C The Autonomic Nervous System, New York, The Macmillan Company, 1935 Telford, E D The Technique of Sympathectomy, *Brit J Surg* **23** 448, 1935

18 Smithwick, R H Modified Dorsal Sympathectomy for Vascular Spasm (Raynaud's Disease) of the Upper Extremity, *Ann Surg* **104** 339, 1936

centage of failures or recurrences after this type of preganglionic section, at present it is possible only to report the marked difference in the upper extremities of the four patients, each of whom had post-ganglionic section on one side and preganglionic section on the other side

3 VASCULAR DISEASES FOR WHICH SYMPATHECTOMY IS PERFORMED NOT BEING DISEASES OF THE VASOMOTOR SYSTEM

While occasional authors¹⁹ report inflammatory or degenerative changes in the ganglions removed by sympathectomy for Buerger's disease and for Raynaud's disease, the consensus is that the removed ganglions do not show any pathologic changes²⁰ Our material has been examined for some time by Dr Hassin, who has not found any histologic evidence of pathologic processes in the excised ganglions or trunks Obviously, sympathectomy operates not by removal of diseased tissue but by alteration of function As pointed out before, in Raynaud's disease the operation inhibits the fluctuations of vasomotor tonus, which may be enough to elicit a spasm in a sensitized or abnormally narrow artery In Buerger's disease it puts the inflamed vessel at rest and interrupts a spinal reflex originating in segmental thrombi It does the same in the reflex dystrophies, in acute osseous atrophy, causalgia or stump neuroma In poliomyelitis with vasospasm the operation may interrupt an efferent vasoconstrictor impulse originating in irritative phenomena of the lateral horn or anterior roots Rarely, however, one may encounter vasoconstrictor phenomena in organic lesions of the sympathetic nervous system, as have been described by Peet and Kahn²¹

4 SLIGHT OR NEGLIGIBLE CLINICAL BENEFIT OF SYMPATHECTOMY

The argument that the clinical benefit of sympathectomy is often slight or negligible calls for an analysis of the causes of failure following sympathectomy Mistaken diagnosis, mistaken indications, improper stages of the vascular disease, faulty technic, improper after-treatment and a poor follow-up are important factors in the obtaining of poor results Summarily expressed, the surgeon who performs sympathectomies must be thoroughly familiar with peripheral vascular disease

19 Kuntz, A Sympathetic Ganglions Removed Surgically A Histopathologic Study, *Arch Surg* **28** 908 (May) 1934 Sunder-Plassmann, P Untersuchungsergebnisse zur Grenzstrangchirurgie, *Arch f klin Chir* **183** 653 (Oct 28) 1935

20 Craig, W M, and Kernohan, J W The Surgical Removal and Histologic Study of Sympathetic Ganglia in Raynaud's Disease, Thrombo-Angitis Obliterans Chronic Infectious Arthritis, and Scleroderma, *Surg, Gynec & Obst* **56** 767, 1933

21 Peet, M M, and Kahn, E A Vasomotor Phenomena Allied to Raynaud's Syndrome, *Arch Neurol & Psychiat* **35** 79 (Jan) 1936

and its remissions and exacerbations, as well as its spontaneous course, and should use, either alone or in collaboration with physicians well versed in peripheral vascular disease, all the medicinal aids and physical therapy available at present. This principle applies to the surgical treatment of the central nervous system, of the endocrine glands and of the gastro-intestinal tract. There is no reason for a surgeon who can approach a sympathetic chain and remove it to be successful when his contact with peripheral circulatory disease is meager.

COMMENT

It is worth emphasizing, then, that surgical treatment of the sympathetic nervous system in cases of peripheral vascular disease is successful when the patients are carefully selected. It does not cure the disease, as does the removal of a diseased appendix or gallbladder, it

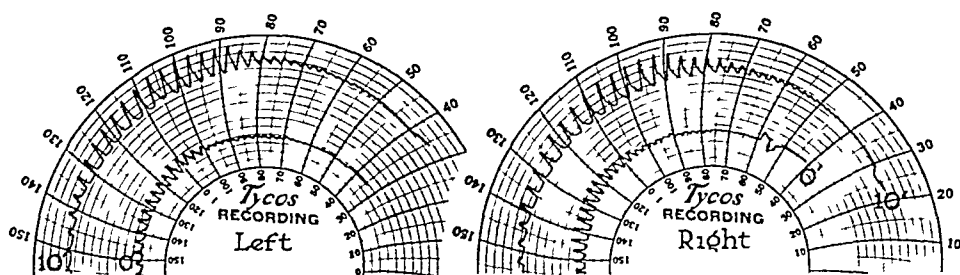


Fig 4—The sodium nitrite test. In A. M., a 31 year old woman suffering from Raynaud's disease of all four extremities, oscillographic curves for the ankles revealed a marked capacity for vasodilatation. The tests were run before and ten minutes after the intravenous administration of a freshly prepared solution of sodium nitrite. One cubic centimeter of 4 per cent solution is now being used routinely in the clinic. Note that ten minutes after the intravenous administration of sodium nitrite the spikes, representing the pulse beats, have increased in height, there is also a shift of these spikes toward the right. The difference is marked between 100 and 90 mm of mercury before and after the administration of sodium nitrite.

only modifies perversions of functions the persistence of which is followed by a greater or lesser degree of organic damage. To test the capacity for dilatation of the vascular bed, a sodium nitrite test has been worked out, the details of which are being published elsewhere (fig 4). This test enables one to eliminate patients who will not benefit from sympathectomy because of the extent of organic damage.

In analyzing the results of sympathectomy for Raynaud's disease (table 3) the following causes of failure have been recognized: (1) a *too advanced stage of disease* (stage 3), characterized by sclerosis of connective tissue, stiffness of the joints, sclerodactylia, ulcerations and inability to open the vascular bed with heat or sodium nitrite (the second and eighth patients belong to this group), (2) *incomplete denervation*, recognizable by residual sweating, usually over the ulnar area in the upper and the femoral-saphenous area in the lower

extremity (this was observed in the second patient of this series), and (3) *postoperative sensitization* due to postganglionic degeneration. The vessels in these areas are increasingly sensitive to epinephrine and solution of posterior pituitary. Since White's important emphasis on this cause of failure, sympathectomy on the upper extremities has always been performed so as to avoid postganglionic degeneration.

In studying the results of sympathectomy in Buerger's disease (table 4), the cause of failure can be found in trying to extend the use of sympathectomy to patients in whom the organic damage is too extensive. After my only fatal sympathectomy, due to coronary thrombosis, electrocardiographic records have been made for every patient with Buerger's disease. This patient (case 1) had extensive vascular damage of the coronary vessels and in the peripheral vessels,

TABLE 3—*Results of Sympathectomy in Raynaud's Disease (Sixteen Sympathectomies on Six Patients) **

Case No	Name	Duration, Years	Stage of Disease	Operation	Result	Comment
1	Wanda F	3	2	Preganglionic 1 Postganglionic 1	Fair 1 Failure 1	
2	Nettie S	8	3	Postganglionic 2	Failure 2	Residual sweating
3	Adeline M	6	2	Preganglionic 1 Postganglionic 1 Lumbar 2	Excellent 3 Failure 1	Brachial neuritis, 6 wk
4	Augusta J	1	2	Preganglionic 1 Postganglionic 1	Excellent 1 Fair 1	
5	Phyllis Z	10	2	Preganglionic 1 Postganglionic 1	Excellent 1 Fair 1	Brachial neuritis, 4 mo
6	Kate S	8	3	Postganglionic 2 Lumbar 2	Fair 2 Excellent 2	

* The patients in this series have been followed through at least one winter (three of them through two winters). By fair result is meant definite improvement, with fewer or shorter attacks, but not complete relief.

with superimposed atherosclerosis. With the exception of this patient, all the patients were less than 40 years old and showed sufficient vasodilatation to heat or sodium nitrite to justify sympathectomy. The most marked effect was obtained on coldness and numbness, then on rest pain and ulceration, intermittent claudication, which in our experience is often improved by intermittent venous hyperemia²² is hardly influenced by sympathectomy. Sympathectomy was performed on the upper extremity to heal ulceration of the fingers or to prevent pulseless cold hands from becoming gangrenous. Collateral circulation here is so much more extensive that the operation can be performed in the presence of much more organic damage on the upper than on the lower extremity.

²² de Takats, G, Hick, F K, and Coulter, John S. Intermittent Venous Hyperemia, in Treatment of Peripheral Vascular Disease, J A M A 108 1951 (June 5) 1937.

The results for the seven patients with causalgia, traumatic osteoporosis or poliomyelitis with vessel spasm are uniformly satisfactory, mainly because organic vascular damage is slight and occurs only late in the course of the disease (table 5). One cannot subscribe to the

TABLE 4—Results of Sympathectomy in Buerger's Disease (Twenty-Two Sympathectomies on Ten Patients)

Case No	Name	Age	Operation	Effect on*				Comment
				Coldness and Numbness	Claudication	Rest Pain	Ulceration	
1	John H	48	Lumbar	2 0	0	0		Died on fifth day of coronary occlusion
2	Maurice V T	31	Preganglionic	2 +++	+	+++		Excellent
3	Sam S	36	Lumbar	2 +++	0	++	+++	Excellent
4	Sol L	39	Lumbar	2 +++†	+	+++		Excellent
5	F N	38	Preganglionic	2 +++	++			Fair on lower, excellent on upper extremities
			Lumbar	2 —	0	---		
6	A T	35	Preganglionic	1 +++	0	++		Bilateral amputation
			Lumbar	2 0	0	0		
7	A R	36	Preganglionic	1 +++	+	+++		Excellent
8	George G	30	Preganglionic	1 +++		+++		Excellent
			Lumbar	1 +++	+	+++		
9	J A	31	Lumbar	2 +++	—	+++		Fair
10	J D	28	Lumbar	2 +++	++	—		Excellent

* +++ indicates complete relief, ++, greatly improved, +, better, 0, no effect, and — absent before operation. Claudication was gaged according to ability to walk at a rate of ten paces in five seconds until cramping occurred.

† Crushing of the peripheral nerve produced this result.

TABLE 5—Results of Sympathectomy for Peripheral Circulatory Disturbances, 1928 to 1935

Diagnosis	Number of Patients	Number of Operations	Number of Operations Followed by			
			Success	Improvement	Failure	Death
Raynaud's disease	6	16	7	5	4	
Buerger's disease	10	22	15	4	2	1
Poliomyelitis	3	3	3			
Reflex dystrophy	5	5	5			
Total	24	46	30	9	6	1

argument, then, that clinical results of sympathectomy are poor. When they are, a mistake has been made somewhere. The factors involved have been enumerated.

SUMMARY

The arguments against sympathectomy have been discussed, and it has been shown that operation on the sympathetic nervous system is worthy of consideration for selected patients with peripheral vascular disease.

ORIGIN OF NEUTROPHILS IN PERNICIOUS ANEMIA (COOKE'S MACROPOLYCYTES)

BIOPSIES OF BONE MARROW

OLIVER P JONES, PH D

MINNEAPOLIS

It has been aptly mentioned by Heck and Watkins¹ that there is little in the American medical literature concerning the value of neutrophils in pernicious anemia as an aid to diagnosis. There is practically nothing in the American literature dealing with the origin of these cells. Cooke,² after studying cells in the peripheral blood for many years, finally advanced three hypotheses to explain the source of large hypersegmented hyperpolymorphic neutrophils in pernicious anemia, which he called macropolycytes I, II, and III. These are the same cells which have been called pernicious anemia neutrophils and have been accurately described by Downey.³ As will be seen later, the various types of macropolycytes described by Cooke are in reality morphologic variations of cells belonging to the same series of pathologic neutrophils.

The origin of these atypical cells was contemplated in the following hypotheses formulated by Cooke.² First, there is some biochemical change in the plasma which causes the cell to age prematurely and become hypersegmented. Second, there may be something amiss with the mechanism which normally eliminates neutrophils from the circulation, thereby producing abnormally matured neutrophils. Third, the polymorphonuclears may be inherently abnormal, owing to a defect in the parent cells, or there may be some single defect in the cellular environment which is responsible for all the changes manifested in the macropolycytes, since after the administration of liver these cells and

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1 Heck, F J, and Watkins, C H. The Neutrophil in Pernicious Anemia, *Am J Clin Path* **3** 263 (July) 1933.

2 Cooke, W E. The Macropolycyte, *J Lab & Clin Med* **19** 453 (Feb) 1934.

3 Downey, Hal. Diseases of the Blood, in Bell, E T. Textbook of Pathology, Philadelphia, Lea & Febiger, 1934.

the abnormal cells of the hemoglobiniferous series disappear. Furthermore, Cooke and Ponder⁴ have stated "There does not appear any doubt that these cells commence life in the blood stream as simple nucleated types." Accordingly these cells would then become hypersegmented as they matured. It is for this reason that macropolycytes ("pernicious anemia neutrophils") have been likened to megakaryocytes of the marrow, because the nucleus is gnarled and the coarse granules are somewhat azurophilic.⁵ Cooke² stated later that they do not resemble any embryonic or adult blood cell and are not exact replicas of the megakaryocyte.

Cooke and Ponder⁴ have assumed that these cells arise from hemocytoblasts, the potentialities of which have been altered by environmental changes. Normally the hemocytoblast may develop into either a granulocyte or a megakaryocyte, but under altered conditions of environment it attempts to differentiate simultaneously along these two lines. Hence, if the bias is megakaryocytic, then a megakaryocytic type of macropolycyte develops. Although Cooke² has stated that he considers these possible modes of origin for macropolycytes, he has cast aspersions on a myeloid origin of the cells, claiming that they might even originate in mesenchymal descendants in the liver or in hemolymph nodes that have undergone abnormal metaplasia. On the other hand, Piney⁶ found that there is morphologic evidence of defective marrow function, in that hyaline leukocytes (monocytes) are always reduced and there is always a varying number of neutrophils of large size with hypersegmented nuclei.

The first investigators seriously to consider the problem of establishing the origin of these abnormal neutrophils in pernicious anemia were Tempka and Braun,⁷ who studied biopsy specimens of the bone marrow of patients with pernicious anemia. Their findings followed closely those anticipated in Cooke's third hypothesis. These workers observed alterations in the myeloblasts, metamyeloblasts (leukoblasts?), promyelocytes, myelocytes and metamyelocytes. The most profound alteration was noted, however, in cells which they interpreted to be "grossere pathologische stabkernige Neutrocyten." The tortuous

4 Cooke, W. E., and Ponder, E. *The Polynuclear Count*, London, Charles Griffin & Co., Ltd, 1927.

5 Cooke, W. E. *The Macropolycyte*, *Brit. M. J.* **1** 12 (Jan. 1) 1927, *Further Observations on the Macropolycyte*, *ibid.* **1** 800 (May 4) 1929.

6 Piney, A. *Pernicious Anaemia. Some Morphological and Etiological Considerations*, *Brit. M. J.* **1** 271 (Feb. 16) 1924.

7 Tempka, T., and Braun, B. *Das morphologische Verhalten des Sternpunktates in verschiedenen Stadien der perniziösen Anämie und seine Wandlungen unter dem Einflusse der Therapie*, *Folia haemat.* **48** 355, 1932.

nuclei in these cells occupy about two thirds of the cytoplasm. The basichromatin is coarse in some places, while in others it may be loosened so that oxychromatic spaces are distinct. Frequently there are vacuoles in the nucleus, and one of the more constant characteristics is the appearance of large cytoplasmic vacuoles. Here and there groups of clear spaces may be seen in the cytoplasm, with transitions to fully developed vacuoles. Patchy, confluent areas of basophilia may appear in light oxyphilic cytoplasm. The granulation is copious, unevenly large and irregularly distributed. In the same cell, adjacent to the neutrophilic granulation, there may be some azurophilic progranulation. These pathologically altered stab forms appear to arise directly from promyelocytes without passing through the intermediate myelocytic and metamyelocytic developmental stages. The evidence for this is that some promyelocytes show pronounced indentations and contractures, and all transitions to the stab form exist. Also, the nuclear structure in the stab form is practically identical with that of the promyelocyte. Tempka and Braun have recognized three types of developing neutrophils in the marrow of patients with pernicious anemia, i. e., large, medium and small elements. These cells are separated from one another not only by their size but by their intrinsic structure, which is most essential for the identification of pathologic forms.

It must be emphasized that the marrow is not entirely composed of these pathologic elements, for normal granulocytic development is also taking place to a lesser degree. From these observations Tempka and Braun were led to conclude that there is a regenerative-degenerative change in the neutrophilic series. Indications of degenerative alterations include structural alterations of the basichromatin, an increased number of damaged cells and the presence of vacuoles. Indications of pathologic regeneration include basophilia of the cytoplasm, azurophilic progranulation, disproportionate developmental stages between the nucleus and the cytoplasm, doubled nuclei and an abnormal cell size.

Other investigators⁸ have more or less confirmed the observations made by Tempka and Braun⁷ on biopsy specimens of bone marrow of patients with pernicious anemia during a relapse. Segerdahl^{8a} has

8 (a) Segerdahl, Elsa. Ueber Sternalpunktionen, Uppsala, Appelbergs Boktryckeriaktiebolag, 1935. (b) Barta, I. Die Bedeutung der Sternalpunktion bei Anämien und über die Beeinflussung des Knochenmarkes durch Leberbehandlung, *Deutsches Arch f klin Med* **171** 565, 1931. (c) Nordenson, N. G. Studies on Bone Marrow from Sternal Puncture, Stockholm, Bortzell's, Esselte, 1935. (d) Rohr, K. Die diagnostische Bedeutung der Sternalpunktion, *Helvet med acta* **1** 713, 1935. Ueber Bedeutung und Ergebnisse der Sternalpunktion, *Praxis* **24** 326 (June 26) 1935. (e) Henning, N. Ueber die bisherigen Ergebnisse der intravitale Knochenmarkuntersuchungen, *Med Klin* **32** 542 (April 17) 1936. (f) Young, R. H., and Osgood, E. E. Sternal Marrow Aspirated During Life. Cytology in Health and in Disease, *Arch Int Med* **55** 186 (Feb.) 1935.

reported that even the nuclei of myeloblasts commence to be polymorphic and may be in the developmental stage of a myelocyte or metamyelocyte, some of which show a tortuous and fantastic shape. Eventually these forms transform into the hypersegmented leukocytes which are often much enlarged. Therefore, hypersegmentation is not a true expression of the age of a cell. Barta^{8b} likewise claimed that hypersegmentation is not a criterion of age but rather an expression of altered function of the bone marrow. Nordenson^{8c} observed that maturation process in promyelocytes and myelocytes is disturbed, causing these cells to become much larger than is normally in keeping with their age. Unlike Segerdahl, Nordenson did not find marked changes in the myeloblast.

Similarly, Rohr^{8d} has reported that the nuclei have a tendency to become hypersegmented and polymorphic during the myelocyte and metamyelocyte stages. Henning^{8e} has found the abnormalities of the neutrophilic series to be the most striking alteration of bone marrow caused by pernicious anemia. Young and Osgood^{8f} reported that "a few multilobulated neutrophils and giant staff cells are present" but made no mention of the regenerative-degenerative changes reported by Tempka and Braun.⁷ In one article Dameshek^{9a} did not mention the abnormal developmental stages of the neutrophil in marrow during pernicious anemia. Later, Dameshek and Valentine^{9b} stated that "the huge bizarre forms of metamyelocytes suggest monstrosities in cellular development." They stated as their belief that these cells are responsible for the hypersegmented neutrophils of the peripheral blood. Others¹⁰ have also found precocious abnormal polymorphism and segmentation of neutrophils in the marrow, which they have claimed explains the cause for the appearance of "pernicious anemia neutrophils" in the peripheral blood. Many other investigators¹¹ have studied

9 (a) Dameshek, W. Biopsy of the Sternal Bone Marrow, *Am J M Sc* **190** 617, 1935. (b) Dameshek, W., and Valentine, E. H. The Sternal Marrow in Pernicious Anemia. Correlation of the Observations at Biopsy with the Blood Picture and the Effects of Specific Treatment in Megaloblastic ("Liver-Deficient") Hyperplasia, *Arch Path* **23** 159 (Feb.) 1937.

10 Jaffé, R. H. The Bone Marrow, *J A M A* **107** 124 (July 11) 1936. Jagic, N., and Klima, R. Zur Klinik und Differentialdiagnose der Anämien mit besonderer Berücksichtigung der Knochenmarkspunktion, *Wien klin Wchnschr* **48** 282 (March 1) 1935. Markoff, N. Die Beurteilung des Knochenmarks durch Sternalpunktion, *Deutsches Arch f klin Med* **179** 113, 1936. Yamamoto, T. Die feinere Histologie des Knochenmarkes als Ursache der Verschiebung des neutrophilen Blutbildes. Vergleichende experimentelle pathologisch-anatomische und klinische Untersuchungen, *Virchows Arch f path Anat* **258** 62, 1925.

11 (a) Arinkin, M. I. Die intravitale Untersuchungsmethodik des Knochenmarks, *Folia haemat* **38** 233, 1929. (b) Doan, C. The Type of Phagocytic Cell and Its Relative Proportions in Human Bone Marrow and Spleen, as Identified by the Supravital Technique, *J Exper Med* **43** 289, 1926. (c) Doan, C., and

the bone marrow of patients with pernicious anemia during a relapse and either have failed to observe these profound alterations of the neutrophilic series or else have neglected to mention them

MATERIAL

The present investigation was carried out on fifteen biopsy specimens of bone marrow from patients with pernicious anemia during a relapse¹² Eight were prepared by smearing freshly aspirated sternal marrow, and seven were dry imprint (*Abklatsch*) preparations All preparations were stained with the May-Grunwald-Giemsa combination stain of Pappenheim The best morphologic detail of the marrow cells was elicited by the dry imprint method, consequently these preparations were studied more intensively than films of aspirated marrow Since this paper is concerned chiefly with the origin of pathologic cells encountered in the peripheral blood, it is obvious that the method of choice would have to be the dry imprint or dry smear method These are the only methods which bring out the finer structural details, especially of the nucleus, which is so important for the proper identification of the immature "lymphoid" cells that have not developed specific cytoplasmic characters

OBSERVATIONS

My previous studies¹³ have revealed that the large neutrophils (macropolycytes) in pernicious anemia have an entirely different life history from that of the neutrophils in normal bone marrow One of the most striking features is the marked anisocytosis and macrocytosis of the leukopoietic elements Leukoblasts and promyelocytes

Zerfas, L The Rhythmic Range of the White Blood Cells in Human, Pathological Leucopenic and Leucocytic States, with a Study of Thirty-Two Human Bone Marrows, *ibid* **46** 511, 1927 (d) Escudero, P, and Varela, M E La biopsia del midollo osseo nelle sue applicazioni in ematologia, *Haematologica*, II Recen **3** 65, 1932 (e) Holmes, W F, and Broun, G O Clinical Study of Bone Marrow by the Method of Sternal Puncture, *Proc Soc Exper Biol & Med* **30** 1306, 1933 (f) Isaacs, R The Bone Marrow in Anemia, *Am J M Sc* **193** 181 (Feb) 1937 (g) Peabody, F W The Pathology of the Bone Marrow in Pernicious Anemia, *Am J Path* **3** 179 (May) 1927 (h) Roversi, A S, and Tanturri, E La puntura dello sterno nella pratica medica, *Haematologica* **16** 1, 1935 (i) Weiner, W, and Kaznelson, P Ueber die zellige Zusammensetzung des Knochenmarkes nach Erfahrungen mittels der Sternalpunktion nach Seyfarth, *Folia haemat* **32** 233, 1926 (j) Heilbrun, N The State of the Sternal Bone Marrow in a Case of Macrocytic (Pernicious) Anemia of Pregnancy, *J A M A* **107** 27 (July 4) 1936

12 This material was made available through the cooperation received from Dr Cecil J Watson and other members of the staff of the department of medicine, the University of Minnesota Medical School

13 Jones, O P (a) Cytological Studies of Biopsied Pernicious Anemia Bone Marrow During Relapse, *Proc Soc Exper Biol & Med* **34** 694, 1936, (b) Cytology of Pathologic Marrow Cells, with Special Reference to Bone Marrow Biopsies, in Downey, H Handbook of Hematology, New York, Paul B Hoeber, Inc, to be published

may be two or three times as large as corresponding normal cells. Another outstanding alteration is found in the complex and bizarre arrangement of the nuclei in various developing neutrophils. On the whole, my observations agree well with those of Tempka and Braun,⁷ but, as will be seen later, the interpretation is different.

Pathologic alterations were found in the myeloblast, leukoblast, promyelocyte and myelocyte stages of development. In some instances the alterations were such that it was extremely difficult to decide to which category a given cell belonged. The earliest change observed in the myeloblast was a slight tendency toward polymorphism. Tempka and Braun⁷ observed an absence of nucleoli in many myeloblasts and said that they considered this to be due to a pathologic alteration. However, I do not attach much significance to this fact, since it has been shown that the presence of nucleoli is variable in myeloblasts.¹⁴ Some myeloblasts were extremely basophilic, almost as basophilic as promegaloblasts, but here again one is dealing with another variable characteristic. Tempka and Braun⁷ have reported a loosening and thickening of the chromatin net in some myeloblasts. This was never observed in my material. Cytoplasmic vacuoles were present in some myeloblasts.

A more pronounced nuclear polymorphism is generally found in the leukoblast stage, which possibly corresponds to the metamyeloblast of Tempka and Braun.⁷ This type of cell, with peculiar protuberances and invaginations of the nucleus, is shown in figure 2*a*. There may be vacuoles in the cytoplasm and some azurophilic granulation. However, many of the leukoblasts of the present series were without azurophilic granulation.

Some large promyelocytes were found with normally shaped nuclei, while in a few cells the nucleus was like a giant band (stab) form (fig 2*b*). Others had a hyperpolymorphic nucleus. Cytoplasmic vacuoles were present, as well as perforations in the nuclear material. Some promyelocytes had coarse azurophilic granulation, while others had only the slightly metachromatic granules of beginning specific neutrophilic granulation. No direct relationship was observed to exist between azurophilic and specific granulations, as Downey¹⁴ has already shown. I¹⁵ have also shown that the presence of azurophilic granules does not necessarily indicate differentiation toward the granulocytic series. These atypical promyelocytes possessed a cytoplasmic basophilia of varying

14 Downey, Hal. (a) The Myeloblast. Its Occurrence Under Normal and Pathological Conditions, and Its Relations to Lymphocytes and Other Blood Cells, *Folia haemat* **34** 65 and 145, 1927, (b) The Myeloblast, in *Handbook of Hematology*, New York, Paul B. Hoeber, Inc., to be published.

15 Jones, O. P. Atypical Azurophilic Granulation in Megaloblasts, *Folia haemat* **55** 195, 1936.

intensity Cells were considered to be in this stage of development as long as there was a reasonable amount of basophilia remaining in the cytoplasm If the cytoplasm contained a full quota of specific granules, the cell was considered to be in the myelocyte stage Since there is such a great disparity between the maturation of the nucleus and that of the cytoplasm, nuclear criteria cannot always be relied on in determining the exact level of development

In the myelocyte stage the atypical neutrophils have a cytoplasm that is completely filled with granules that are more acidophilic and larger than normal Cytoplasmic vacuoles may be present, but as a

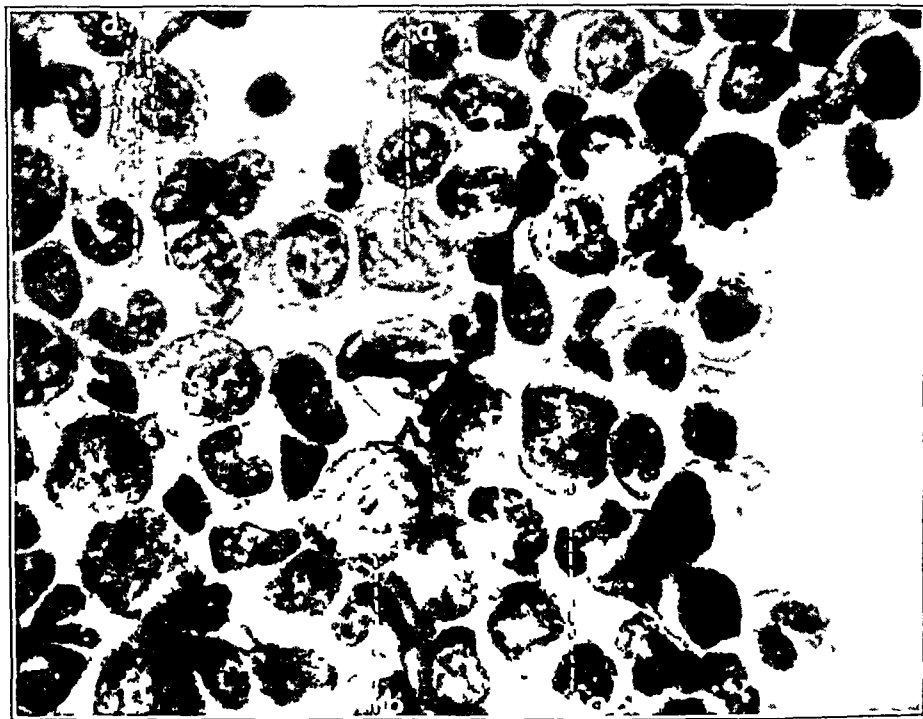


Fig 1—Imprint of fresh rib marrow obtained from a patient with chronic empyema This particular marrow was selected rather than normal marrow because, even though there is a marked increase in metamyelocytes and band forms, they are never as large or polymorphic as the cells shown in figures 2 and 3 *a* indicates a pronormoblast (pro-erythroblast) Cells similar to this are undoubtedly the ones Doan and Zervas^{11c} misinterpreted for "megaloblasts" *b* indicates a normal neutrophilic promyelocyte *c* indicates a normal neutrophilic myelocyte, *d*, normal neutrophilic metamyelocytes Compare *b*, *c* and *d* with the pathologic cells shown in figures 2 and 3 May-Grunwald-Giemsa stain The magnification is the same for figures 1 to 3

rule these tend to disappear during this stage of development Therefore, the presence of vacuoles in earlier stages of development is indicative of an abnormal maturation rather than a sign of degeneration The nuclear configuration is complex and bizarre (fig 2 *c*) Generally the

arrangement of chromatin is less compact than that of corresponding stages in the normal neutrophil. Some of these atypical myelocytes may have one or more perforations in the nuclear material, in addition to a hyperpolymorphic configuration. These holes in the nucleus commence as areas of rarefaction and ultimately become a single, definitely circumscribed hole (fig 3 *a*). In cross-section the perforations appear initially as invaginations in the nuclear mass. The actual perforation occurs after opposite invaginating nuclear membranes come in contact. Some myelocytes (fig 3 *a*) have a single large circular hole, which gives them the appearance of a torus (doughnut). Other pathologic neutro-

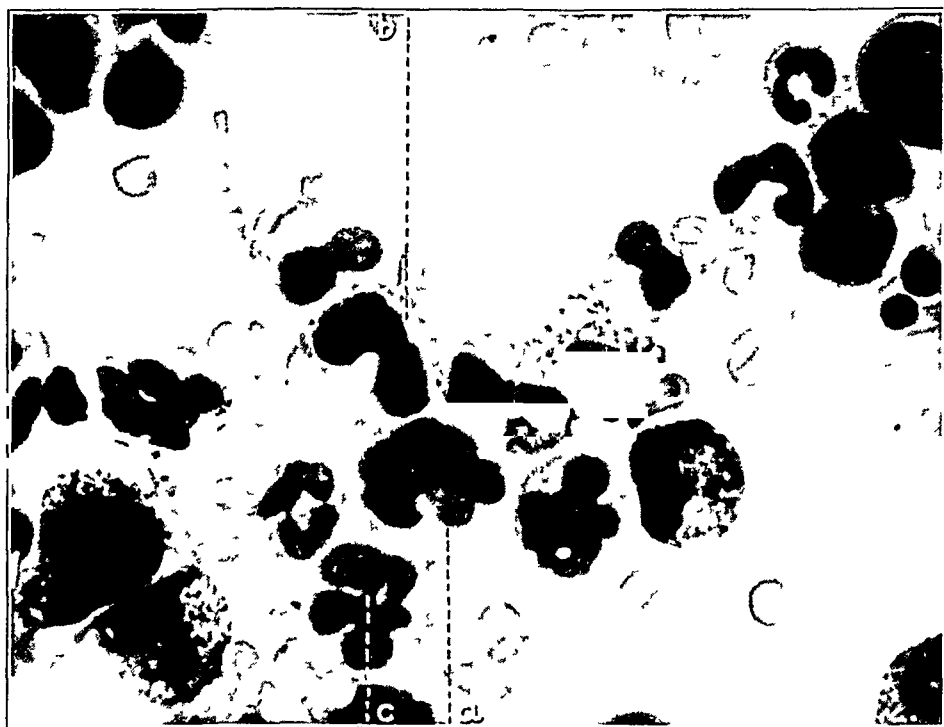


Fig 2—Imprint of marrow obtained for biopsy from a patient with pernicious anemia during a relapse. *a* indicates a hyperpolymorphic leukoblast with several areas of rarefaction in the cytoplasm, *b*, an atypical promyelocyte of the neutrophil series in pernicious anemia. The cytoplasm is faintly basophilic and contains two vacuoles and early neutrophilic granulation. The nucleus is like a giant band form. *c* indicates an older atypical myelocyte. Note the peculiar nuclear protuberances. May-Grunwald-Giemsa stain.

philic myelocytes are found to have three or more holes in the nucleus, separated from one another by a strand of chromatin which varies in thickness. These nuclear perforations may develop to such an extent that they are finally bounded on two sides by a thin strand of chromatin. Not all the atypical neutrophilic myelocytes undergo a nuclear perforation during maturation. Instead, some develop elongated, band-shaped nuclei (fig 3 *b*). These cells have been described by Tempka

and Braun⁷ as *grosse pathologische stabkeimige Neutrocyten*. In these forms the nucleus may become so twisted and convoluted that there is overlapping. These alterations have been interpreted by Tempka and Braun⁷ as indicating degenerative manifestations. Contrary to this, I believe that these nuclear changes express the manner in which the pathologic neutrophilic myelocyte ultimately attains the morphology of "macropolycytes II and III" described by Cooke² or the "pernicious anemia neutrophil" of the peripheral blood described by Downey³.

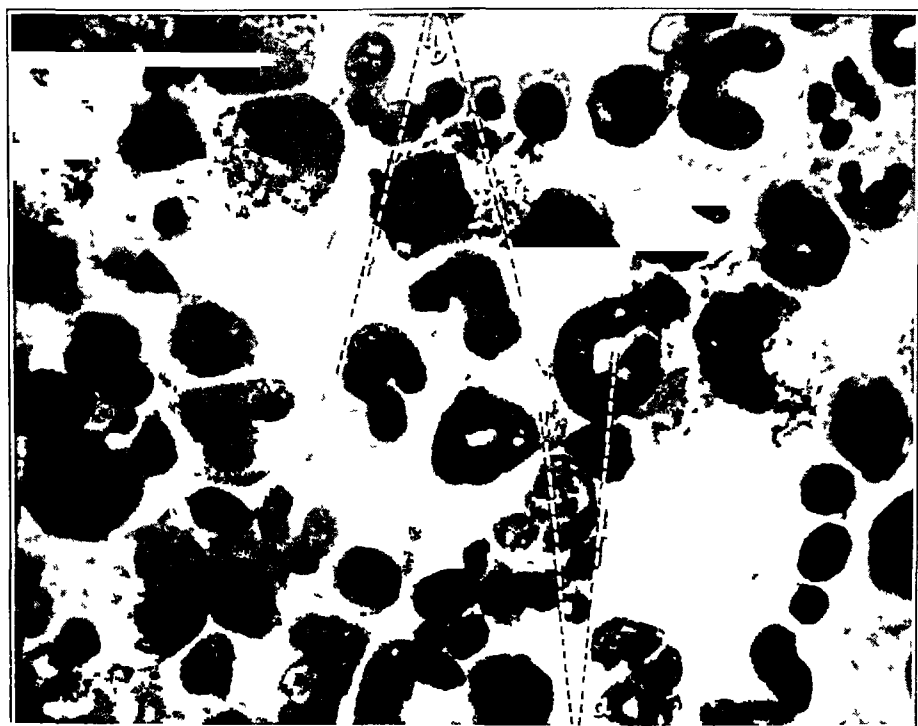


Fig 3—Imprint of marrow obtained for biopsy from a patient with pernicious anemia during a relapse. *a* indicates atypical neutrophilic myelocytes showing the peculiar perforations of nuclear material, *b*, atypical neutrophilic myelocytes with large band-form nuclei. Note the other hyperpolymorphic neutrophils in the field and compare these with normal-sized metamyelocytes and band forms in figure 1. May-Grunwald-Giemsa stain.

From the foregoing description it can be seen that I was able to find abnormalities in every stage of neutrophilic development. This is contrary to the observations made by Dameshek and Valentine,^{9b} who found maldevelopment occurring only in the neutrophilic metamyelocytes and occasionally in myelocytes. However, their figures do not support this contention. Their cells *a* and *b* in figure 4 appear to have a basophilic cytoplasm with few granules. My interpretation is that

these cells represent promyelocytes (as determined by the cytoplasm) which have undergone a precocious nuclear polymorphism

COMMENT

Since it has been shown that the neutrophils seen in pernicious anemia are important as an aid in the diagnosis of macrocytic anemias,¹⁶ it seems only natural that considerable attention should be directed toward the determination of the origin of these neutrophils. My observations and those which were mentioned in the review of the literature furnish ample evidence to indicate that the hyperpolymorphic and hypersegmented neutrophils in the peripheral blood of patients with pernicious anemia do not enter the blood as simple nucleated forms. Furthermore, studies of the bone marrow of patients with pernicious anemia have revealed that these neutrophils have a life history (ontogeny) which is abnormal throughout and different from that found in normal human marrow. While the marrow undoubtedly produces the majority of these pathologic neutrophils, it cannot be denied that these neutrophils may also be produced to a limited extent in other organs as a result of myeloid metaplasia.

It is significant that the neutrophils seen in pernicious anemia are not merely functional alterations of normal neutrophils, such as the "toxic" and pathologic neutrophils encountered in the peripheral blood in certain septic conditions. I believe it is justifiable to assume that there is a true pathologic regeneration of neutrophils in the marrow in pernicious anemia during a relapse which results in the production of a pathologic neutrophilic series. The morphologic evidence for this assumption is as follows: the precocious nuclear polymorphism, the nuclear pattern which is different from normal, cells two to three times larger than normal, granules larger and more acidophilic than normal, the cytoplasmic vacuolation and the nuclear perforation. (This whole process reminds one of the granulocytic development which sometimes proceeds from Rieder cells in the leukemias.) There are no signs of "toxic degeneration," such as pyknotic nuclei and "toxic" granulation, in these pathologic neutrophils.

There is considerable variation in the nuclear configuration of neutrophils which have been produced by this pathologic regeneration. This is due to the fact that precocious nuclear polymorphism may commence in the leukoblast, the promyelocyte or the myelocyte stage. Therefore, the more mature forms of neutrophilic development have nuclei exhibit-

16 (a) Heck and Watkins¹ Downey² (b) Fallon, M. Classification of the Anemias, Blood Pictures of the Anemias and Anemias in Infancy and Childhood, in Downey, H. Handbook of Hematology, New York, Paul B. Hoeber, Inc., to be published

ing various degrees of complexity. Then, too, all the pathologic neutrophils do not pass through a stage of development in which there are perforations in the nuclear material. The "macropolycytes I, II and III" described by Cooke are in reality morphologic variants of the same pathologic neutrophilic series. Hence, there is no necessity for subdividing the neutrophils of pernicious anemia into three different types, but it is essential to recognize the many morphologic forms they may assume. Since these forms have been adequately described by Heck and Watkins,¹ Downey³ and Fallon^{16b} elsewhere, repetition is not necessary here.

If it is concluded that the relative age of neutrophils can be determined by the degree of nuclear segmentation, then one must assume that the neutrophil of pernicious anemia has actually undergone precocious senility in the marrow. This condition may be the result of a faulty mechanism of delivery which causes the cells to remain in the marrow longer than normal. However, it seems more likely that hypersegmentation in these neutrophils is an indication of an alteration in the function of the bone marrow beginning in the earliest stages of neutrophilic development, rather than a criterion of age.¹⁷ The evidence at hand indicates that the neutrophils of pernicious anemia have a hyperpolymorphic nucleus before they enter the blood stream, but it cannot be denied that these cells may continue to become even more polymorphic after they have once entered the blood stream. It is on the basis of this extreme nuclear polymorphism that the neutrophils (macropolycytes) of pernicious anemia have been likened to megakaryocytes.¹⁸ Even at best, this similarity is superficial, for at no time during the course of their development do these pathologic neutrophils have a chromatin pattern simulating that of a megakaryocyte.

It is paradoxical that a lack of the principle potent against pernicious anemia should cause the production of giant neutrophilic promyelocytes and myelocytes as well as the much enlarged forms of the megaloblastic series. Some investigators have thought that the oligocythemia in pernicious anemia is caused by a blocking of the marrow with megaloblasts. In the same manner the leukopenia of pernicious anemia might be explained as the result of the blocking of the bone marrow with giant neutrophils. Davidson and Gulland¹⁹ have advanced certain ideas

17 N. von Jagic and R. Klima have recently stated that the cells are not over aged, as was formerly assumed, but as a result of the premature onset of segmentation they are too extensively segmented (*Ueber die diagnostische Bedeutung der Knochenmarkpunktion*, Wien klin Wchnschr 50 363 [March 19] 1937).

18 Cooke and Ponder.⁴ Cooke.⁵

19 Davidson, L. S. P., and Gulland, G. L. *Pernicious Anaemia*, London, Henry Kimpton, 1930.

concerning the nature of leukopenia in pernicious anemia which I believe are worthy of quoting They have said

Considering the vast increase in the amount of active marrow in this disease, the number of marrow leucocytes must be greatly in excess of the normal In view of this it is difficult to explain the constant leucopenia and the rarity of leucocytosis, even in the presence of severe septic complications, unless one assumes that the absence of the specific liver factor in some way interferes with the passage of leucocytes into the blood, or with the transformation and maturation of myelocytes into the polymorphonuclear forms The latter seems the more likely, and we suggest that liver is responsible not only for the proper performance of the normoblastic function, but also for the ripening of the neutrophilic leucocytes

Storti²⁰ has differed with Davidson and Gulland by claiming that there is a reduction in the total leukopoietic tissue at the expense of the more mature forms and that there is complete disappearance of hemocytoblasts (myeloblasts) He has interpreted this to indicate a tendency toward arrest of maturation Vladoš and Bondarenko²¹ have also reported an arrest of leukopoietic activity during a relapse

If there is an arrest of maturation in pernicious anemia, it certainly is not similar to the arrest which Fitz-Hugh and Krumbhaar²² and Darling, Parker and Jackson²³ found in agranulocytosis At present there is no suitable explanation for the leukopenia in pernicious anemia One or all of the aforementioned factors may play a part in its production, or it may be due to what Naegeli²⁴ has called biologic torpor of the bone marrow

Since the advent of liver therapy for pernicious anemia a great deal of attention has been directed toward the so-called inhibition of differentiation at the "megaloblast stage" during relapse Also, in the field of experimental hematology attempts have been made to produce macrocytic anemia with a megoblastic bone marrow So much consideration has been given to this one particular condition of the marrow that the exact status of other myeloid components has been neglected by the majority of American workers

Although various investigators have suggested or assumed that there is an involvement of the entire marrow, rather than just the hemoglobiniferous cells, Tempka and Braun⁷ were the first to make a

20 Storti, E Studio in vivo del midollo osseo nell' anemia perniciosa, *Haematologica* **18** 1, 1937

21 Vladoš, C, and Bondarenko, E Étiologie et pathogénie de l' anémie de Biermer, *Sang* **8** 369, 1934

22 Fitz-Hugh, T, and Krumbhaar, E B Myeloid Cell Hyperplasia of the Bone Marrow in Agranulocytic Angina, *Am J M Sc* **183** 104, 1932

23 Darling, R C, Parker, F, and Jackson, H The Pathological Changes in the Bone Marrow in Agranulocytosis, *Am J Path* **12** 1 (Jan) 1936

24 Naegeli, O Ueber die Entstehung und Behandlung der Anamien, *Wien klin Wchnschr* **48** 225 (Feb 22) 1935

qualitative study of other myeloid cells. They found that there is a panmyelopathy in pernicious anemia during a relapse. This consists of the appearance of numerous cells belonging to the pathologic hemoglobiniferous series, i e, promegaloblasts and megaloblasts and megakaryocytes, numerous "grosse stabkernige Neutrozyten," with the variegated picture of degenerative-regenerative transformations, and severe impairment of the megakaryocytic system. They found that lymphocytes were also effected in the majority of cases. These were not only increased in number but in some instances showed nuclear pyknosis.

Tempka and Braun's concept of panmyelopathy of the marrow in pernicious anemia during a relapse has been recently confirmed by Dameshek and Valentine^{9b} and myself¹³. However, the interpretation which I have finally given this panmyelopathy is different from that of Tempka and Braun. I agree that the lack of principle potent against pernicious anemia causes a proliferation of a pathologic red cell series, the megaloblasts. This series has its early stages of development as well as hemoglobin-bearing megaloblasts^{13b}. The latter illustrates that there is not an inhibition of differentiation at the so-called "megaloblast stage," contrary to the general belief in this country. Cells of the normoblastic or definitive series are present, but their maturation is inhibited. (It is interesting to note that Storti²⁰ found the number of normoblastic cells to be equal to or even greater than the number in normal bone marrow.) I do not agree regarding the alterations in the neutrophils, which, according to my view, are not degenerative manifestations. The neutrophilic series is affected to the extent that there is developing in the marrow a pathologic series which gives rise to the abnormal neutrophils (macropolycytes) of the peripheral blood of patients with pernicious anemia. Also, the megakaryocytes are not as severely damaged or degenerated as Tempka and Braun have claimed, but they are pathologically altered so that they are not producing platelets^{13b}. No doubt the lymphocytes may also be affected as reported²⁵. Unfortunately I have not made any detailed studies of the lymphocytes as yet and therefore cannot confirm these observations.

At present I am unable to state whether the aforementioned pathologic neutrophilic series is limited solely to anemias due to deficiency of liver principle or whether the neutrophils are found in the marrow in other pathologic conditions also. Tempka and Braun⁷ have claimed that these cells are not specific for pernicious anemia, since they found them in the marrow of patients with lymphogranuloma, carcinoma of the stomach and myelogenous leukemia. On the other hand, Norden-son^{8c} claimed that the cytoplasmic and nuclear vacuolation of the

25 Tempka and Braun⁷ Dameshek and Valentine^{9b}

neutrophils is almost pathognomonic of pernicious anemia. Furthermore, Henning^{8c} has reported the pathologic neutrophils to be the most striking alteration of the bone marrow in pernicious anemia.

It is obvious from these studies that a lack of the principle potent against pernicious anemia produces a profound effect on the entire bone marrow. They also show that there is definitely more at fault than a failure of red blood corpuscles to differentiate from the so-called megakaryoblast stage. Further study may reveal that a lack of the principle potent against pernicious anemia has its primary effect on the myeloblast (stem cell) or even the reticulo-endothelium.²⁶

Dr. Hal Downey was a constant source of help and advice throughout the course of this investigation.

26 The Italian school of hematology (Ferrata, di Guglielmo, Villa, Introzzi and Storti) has maintained that there is a systemic disturbance of the connective tissue involving the "hemohistioblasts" in pernicious anemia. Recently Storti²⁰ reported that hemocytoblasts (myeloblasts) were absent from the marrow during relapse and offered this observation as further proof of the "histioid" or mesenchymal nature of pernicious anemia. However, we do not believe this condition has been proved, since Ringoen (*Folia haemat* **33** 149, 1927) has shown that "hemohistioblasts" are artefacts and that these are the cells on which the Italians have formulated their theory. In our material there was no evidence that neutrophils were formed directly from the reticulo-endothelium without passing through the myeloblast stage.

THE HEART IN ACUTE NEPHRITIS

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The effect of acute glomerulonephritis on the heart has received little study in this country in recent years. Yet in 1879 Goodhart¹ pointed out the occurrence of heart failure in this disease and reported dilatation of the heart at necropsy, with fatty degeneration of the cardiac muscle in one case. Other authors confirmed the clinical observation and, notably Volhard and Fahr,² emphasized the frequency of dyspnea, orthopnea and pulmonary edema. Levy³ cited the literature up to 1930 and described additional cases in which the presenting symptoms were those of heart failure. In agreement with the majority of previous writers on the subject, he ascribed the cardiac failure to strain placed on the heart by the sudden onset of hypertension in acute nephritis. Further study of the disease, however, suggested that there is also a widespread vascular lesion not confined to the kidney.⁴ For not uncommonly patients with minimal renal involvement, as evidenced by albuminuria and hematuria, present the severest degree of cardiac insufficiency, which may even lead to death. Furthermore, hypertension or edema may be the initial sign of the disease, indicating a universal vascular disturbance. On the assumption, therefore, that organic changes are present in the heart, we took repeated electrocardiograms in cases of acute nephritis several years ago. Striking abnormalities were encountered, and a preliminary report was made.⁵ Subsequently

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1 Goodhart, J F. On Acute Dilatation of the Heart as a Cause of Death in Scarletinal Dropsy. Five Cases, *Guy's Hosp Rep* **24** 158, 1879

2 Volhard, F, and Fahr, T. *Die Brightsche Nierenkrankheit*, Berlin, Julius Springer, 1914, p 118

3 Levy, I J. The Cardiac Response in Acute Diffuse Glomerulo-Nephritis, *Am Heart J* **5** 277, 1930

4 Fishberg, A M. *Hypertension and Nephritis*, ed 1, Philadelphia, Lea & Febiger, 1930, p 320

5 Master, A M, Jaffe, H L, and Dack, S. The Electrocardiogram in Acute Nephritis, *Am Heart J* **12** 244, 1936

several European authors studied the heart in this disease Marcolongo⁶ observed cardiac dilatation in every patient investigated roentgenographically when hypertension was present Alsina-Bofill⁷ found dyspnea a constant symptom in these patients Twenty per cent of the patients studied by Ellis⁸ exhibited cardiac insufficiency In thirteen patients followed electrocardiographically as well as clinically Tur⁹ independently observed changes in the T wave similar to those found by us Langendorf and Pick¹⁰ also reported abnormalities in the T wave in thirteen patients The T wave became inverted in leads I and II and upright in lead IV, simultaneously the T_s became pointed The authors were impressed with the specificity of the changes and the simulation of the electrocardiogram obtained in anterior infarction

The present report attempts to correlate the electrocardiographic changes with the clinical course in acute glomerulonephritis (table 1) It is based on a study of twenty-four patients with typical involvement for whom electrocardiograms were taken at frequent intervals, the average number being seven The series is not consecutive, for patients with only occasional records have been excluded, hence our results do not express quantitative relationships In almost all cases precordial leads were taken in addition to the three standard limb leads, a few patients were studied prior to the introduction of the use of the precordial lead

The following report will serve to illustrate the characteristic clinical and electrocardiographic findings

R W, a Negro porter 27 years of age, had an unimportant previous history except for gonorrhea Four weeks before admission to the hospital he contracted an infection of the upper respiratory tract which lasted two days He felt well for a week, until he suddenly became dyspneic while attempting to push a cart This symptom disappeared after rest but recurred several days later when he was walking Thereafter he suffered frequent attacks of nocturnal dyspnea and was unable to climb one flight of stairs He complained also of weakness and palpitation One week after the onset of dyspnea the urine became darker However, he continued to work for several weeks, until he noticed swelling of the legs and puffiness of the eyelids and the dyspnea became severe

On admission to the hospital the patient was acutely dyspneic and orthopneic and moderately cyanotic The eyelids were puffy The arteries of the fundus were of normal caliber The tonsils were injected Moist râles were present at

6 Marcolongo, F Il cuore nella glomerulonefrite acuta diffusa, Arch per le sc med **59** 975, 1935

7 Alsina-Bofill, J El corazón en la glomerulonefritis aguda, An de med int **4** 1035, 1935

8 Ellis, A W. M Heart Failure in Acute Nephritis, Quart J Med **5** 533, 1936

9 Tur, A Electrocardiographic Studies in Acute Diffuse Glomerulonephritis, Klin med **13** 1372, 1935

10 Langendorf, R, and Pick, A Elektrokardiogramm bei akuter Nephritis, Med Klin **33** 126, 1937

the base of each lung The heart was enlarged to the left, the apical impulse being forceful and palpable in the sixth interspace, 1 cm to the left of the midclavicular line There was gallop rhythm at the apex, and the sounds were of poor quality The second pulmonic sound was accentuated and louder than the second aortic

TABLE 1—*The Heart in Nephritis*

Case	Age	Highest Blood Pressure, Mm of Hg	Cardiac Symptoms	Lungs	Heart	Electrocardiographic Findings
1	27	190/100			S ₁ split, systolic murmur	T ₁ inverted T ₂ flat, wide P wave
2	32	180/90	Dyspnea, orthopnea	Pleural effusion	Gallop, P ₂ >A ₂ , mitral configuration	Preponderance of left ventricle
3	15	134/100	Dyspnea, orthopnea	Pulmonary edema	Enlarged to left, P ₂ >A ₂ , S ₁ booming	T ₁ cove plane, T ₂ inverted
4	27	200/140	Dyspnea, orthopnea, cyanosis	Rales	Enlarged to left, gallop, poor sounds, P ₂ >A ₂	T ₁ cove plane, T ₂ inverted, T ₄ upright and pointed, P wave notched and high absent initial positive deflection
5	32	190/130			S ₁ split, P ₂ >A ₂	T ₁ inverted, T ₂ semi inverted
6	15	176/96			P ₂ >A ₂	T ₁ , T ₂ and T ₃ high and pointed, PR, 0.22 second
7	39	160/105	Dyspnea		P ₂ >A ₂	T ₁ and T ₂ low
8	28	150/94			Poor sounds	PR, 0.24 second, P wave wide and notched
9	37	168/106				No abnormality
10	34	160/108	Dyspnea			T ₁ , T ₂ and T ₄ high and pointed, PR, 0.22 second
11	14	176/110			Enlarged	T ₁ low, PR, 0.2 second
12	31	150/90				T ₁ low, T ₂ semi inverted, T ₄ diphasic
13	41	180/100	Dyspnea	Pulmonary edema	Enlarged gallop sounds split, P ₂ >A ₂	T ₁ low, T ₂ iso-electric, T ₄ upright, PR, 0.2 second
14	14	142/74		Pleural effusion	P ₂ >A ₂	T ₁ and T ₂ diphasic
15	32	148/98				No abnormality
16	40	170/60	Dyspnea orthopnea	Pulmonary edema	Enlarged	Auricular flutter, T ₁ diphasic, T ₂ inverted
17	29	130/92			Enlarged	T ₁ low, T ₂ semi inverted, T ₄ diphasic
18	24	184/106			P ₂ >A ₂	T ₂ low, T ₄ diphasic P wave high and notched
19	15½	160/100			Enlarged, P ₂ >A ₂	T ₁ T ₂ and T ₄ high and pointed Q ₁ present, small initial positive deflection
20	13	142/80			S ₁ split	T ₁ low
21	40	156/80				T ₁ pointed
22	45	170/90	Dyspnea, orthopnea	Pulmonary edema		Preponderance of left ventricle
23	40	200/100	Dyspnea orthopnea	Pulmonary edema		T ₁ and T ₄ low initial positive deflection absent
24	17	150/90			Enlarged	No abnormality

sound The heart rate was 110, and the blood pressure was 200 systolic and 140 diastolic There was pitting edema of the legs The venous pressure measured 6 cm of water, the arm to tongue circulation time was twenty-two seconds and the vital capacity was 1,600 cc—evidences of isolated failure of the left ventricle

The urine contained 3 plus albumin and numerous red blood cells and casts. The urea nitrogen content of the blood was 14 mg per hundred cubic centimeters.

Phlebotomy was performed, and the patient was allowed neither fluids nor food. Improvement was rapid, by the next day the dyspnea, râles in the lungs, tachycardia and gallop rhythm had disappeared. He continued to do well, the heart became smaller and the blood pressure returned to normal. The arm to tongue circulation time diminished to sixteen seconds, and the vital capacity rose to 2,750 cc. On the thirteenth day, however, the blood pressure suddenly rose to 150 systolic and 100 diastolic, the heart began to enlarge again, the apical sounds became poor, a rough systolic murmur was heard over the pulmonic area and the second pulmonic sound became accentuated. There were numerous premature beats. With limitation of fluids, all these signs disappeared in one day, and the patient went on to complete recovery.

When the patient was admitted to the hospital the electrocardiogram (fig 1, Dec 18) showed sinus tachycardia, preponderance of the left ventricle, a prominent notched P wave, slight slurring of the QRS complex, absence of the initial positive deflection in the precordial lead and low voltage of the T wave. Five days later the rate was slower, and there was no preponderance. The initial positive deflection had reappeared. Wave T_1 was inverted and cove-plane, T_2 slightly inverted and T_4 deeply negative and pointed. The changes in the T wave were similar to those seen in anterior infarction. Ten days later preponderance of the left ventricle was again present, waves T_1 and T_4 were diphasic and wave T_2 was upright.

Comment—In summary, this patient with acute glomerulonephritis presented for several weeks only evidence of failure of the left ventricle, that is, increasing dyspnea and hypertension. Signs of renal disease appeared later. On admission to the hospital he showed signs of advanced insufficiency of the left ventricle, associated with which were changes in the electrocardiogram indicative of myocardial damage. With active treatment the failure of the left ventricle rapidly disappeared, except for a transient recurrence. The changes in the electrocardiogram became more definite but had begun to regress before he was discharged. Although there was severe involvement of the myocardium from the onset, at no time was there evidence of more than moderate renal impairment.

CLINICAL DATA

The majority of the twenty-four patients were young adults, the average age being 27, and the range from 13 to 45 years. The sexes were almost equally represented.

In two thirds of the patients an infection of the upper respiratory tract, usually tonsillitis, preceded the onset of the acute nephritis. The latter was usually evidenced by hematuria and edema, but in two patients the initial symptom was severe dyspnea, so that primary cardiac disease was simulated. In four other patients dyspnea was a prominent and early complaint. These findings confirm the observations of Baehr¹¹ that symptoms of heart failure often occur early in the course of acute glomerulonephritis, before there is extensive renal damage.

11 Baehr, G. Personal communication to the authors.

In the examination of these patients a constant finding was systolic and diastolic hypertension, the highest reading being 200 systolic and 140 diastolic (table 1) The slightest elevation of blood pressure, 142 systolic and 80 diastolic, was obtained for a boy of 13, at this age such a reading is definitely abnormal In each case the hypertension was already present when the patient was first observed Hypertension is one of the earliest signs In several cases the blood pressure dropped quickly, more often it returned to a normal level by the end of the first

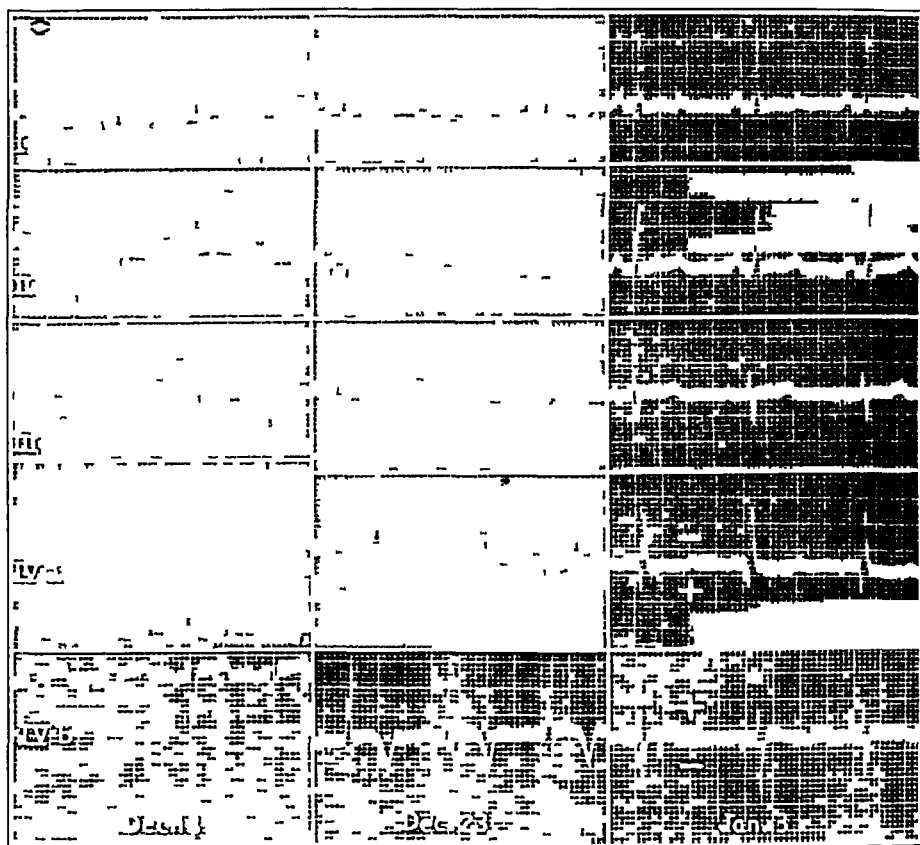


Fig 1 (case 4, a man aged 27) —Dec 18 Sinus tachycardia, pulse rate, 110, preponderance of the left ventricle, wide and prominent P wave, slurring of QRS, practically iso-electric T wave, initial positive deflection absent in the chest lead In this and the succeeding figures lead IV *a* is the chest lead in which waves of positive polarity are directed downward and lead IV *b* is the chest lead arranged so that positive waves are directed upward Dec 23 Pulse rate, 80, no preponderance of left ventricle, the voltage of the QRS complex is higher, P wave, notched, T₁, inverted and cove-plane, T₂, semi-inverted, T₃, upright In the chest lead the initial positive deflection is present, the T wave is of negative polarity Jan 3 Preponderance of the left ventricle is again present P wave, no longer notched, T₁, becoming upright, T₂ and T₃, normal, T₄, iso-electric

or second week, but in five patients it was still at the upper limit of normal on discharge, when recovery was otherwise complete Associated with the hypertension in one third of the patients was moderate

enlargement of the heart to the left, as determined by percussion. This figure is undoubtedly too small, for few of the patients were examined roentgenologically. As the blood pressure fell the size of the heart diminished (fig 2). Other evidence of cardiac involvement included a systolic murmur in nine patients, which usually disappeared, and frequently alterations in the heart sounds, which were booming, poor or split for varying periods.

In addition to these findings, eight patients presented definite evidence of failure of the left ventricle, that is, dyspnea and orthopnea, gallop rhythm, accentuated second pulmonic sound, pulmonary congestion and, in five instances, pulmonary edema. Furthermore the vital capacity was considerably reduced in two patients tested, and in one of these the arm to tongue circulation time was prolonged. Pulmonary edema was usually sudden in onset and severe. In several cases death



Fig 2 (case 24, a boy aged 17)—Cardiac enlargement during the first week of acute nephritis, progressive diminution in size to normal, elevation of blood pressure until March 2, normal thereafter, ranging between 120 systolic and 80 diastolic and 106 systolic and 70 diastolic, normal electrocardiogram. *A* was taken on March 1, *B*, on March 8, and *C*, on March 26.

seemed imminent and was averted only by prompt treatment. The edema occurred only during the stage of hypertension, that is, early in the course of the disease. In two patients it recurred.

Contrary to the statement of Levy³ that failure of the right ventricle is primary, in none of our patients was there unequivocal clinical evidence of this failure, such as dilatation of the veins of the neck or enlargement of the liver. Nor is this surprising, since hypertension increases the work of the left ventricle alone. The significance of edema, ascites or pleural effusion, findings usually indicative of failure of the right ventricle, was necessarily difficult to determine for our patients. However, these features were probably largely the result of the disturbance of water metabolism due to the systemic capillary injury and not to heart failure, for the highest venous pressure reading obtained was 9 cm in four cases. This figure is the upper limit of normal and is not sufficiently high for a definite diagnosis of heart failure. This

interpretation is even more probable in view of the fact that in two of the patients with a venous pressure of 9 cm there was no other evidence of heart failure. Furthermore, for the patients with the most advanced degree of failure of the left side of the heart the venous pressure was normal, as in the case cited.

There were two fatal cases in this series, and in both instances there was failure of the left ventricle. One of these patients was a girl of 14 who was apparently recovering when she died suddenly on the twelfth day. The other was a man of 40 with long-standing rheumatic cardio-valvular disease who showed a progressively downhill course. He died in uremia, postmortem examination revealed no evidence of acute myocardial or endocardial disease.

ELECTROCARDIOGRAPHIC FINDINGS

The electrocardiogram was significantly abnormal at some period of the disease in nineteen patients, in three no change occurred and in the

TABLE 2—*Electrocardiographic Changes in Nephritis*

	Number of Cases
Sinus tachycardia	7
Sinus bradycardia	3
Ventricular premature beats	1
Auricular premature beats	2
Auricular flutter	1
Abnormalities of P wave	4
Prolonged PR interval	5 (longest, 0.24 second)
Preponderance of left ventricle	9 (3 transient)
Low voltage of QRS	5 (2 transient)
High voltage of QRS	2
Slurring of QRS	6 (2 transient)
Large Qs present	3 (did not change)
Absent initial positive deflection in chest lead	3 (2 became small, 1 normal)
RT elevated	2 (slight)
T wave high and pointed	4
T wave low	4
T wave iso electric to inverted	10

remaining two preponderance of the left ventricle alone appeared soon after observation. As will be seen in table 2, the chief abnormalities involved the T wave and, to a less extent, the auriculoventricular conduction time (PR interval) and the initial positive deflection in the precordial lead. Except for premature beats, the only significant arrhythmia was a single instance of auricular flutter. Several authors¹² have emphasized the frequency of bradycardia during the acute stage, we observed this in only a minority of patients. It is true that the pulse rate did not rise above 110 unless there was severe failure of the left side of the heart. Preponderance of the left ventricle was present in nine patients, but in only three did this appear or disappear while they were under observation (fig. 1). Low or high voltage and slurring of

¹² Marcolongo⁶ Alsina-Bofill⁷

the QRS complex were encountered frequently (figs 3) but often were constant. In one of five patients with prolongation of the PR interval this was the only abnormality in the electrocardiogram. The longest interval was twenty-four hundredths of a second. In three cases the PR interval returned to normal, in the remaining two it became shortened but persisted at from one fifth to twenty-two hundredths of a second. In four cases the P wave was high, wide or notched (figs 1 and 4 A). This was interpreted as evidence of failure of the left ventricle with dilatation of the auricles.¹³

The abnormalities in the T wave, however, were most striking, occurring in eighteen patients. There were two types of changes. In

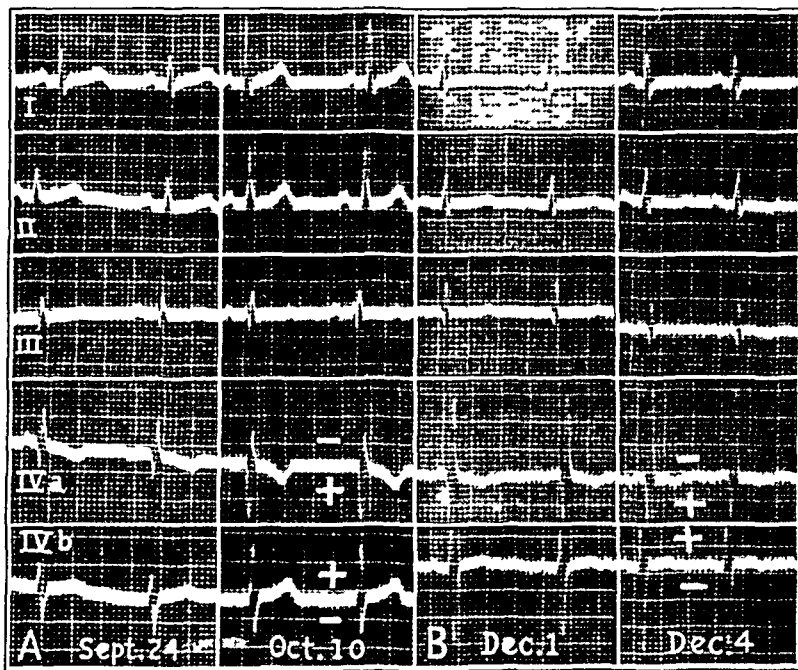


Fig 3—A, case 15, a woman aged 32. Sept 24. Low voltage and slurring of the QRS complex in all leads. Oct 10. QRS complex of normal voltage, higher T wave. B, case 20, a girl aged 13. Dec 1. QRS complex and T wave of low voltage. Dec 4. Slightly higher voltage of QRS, T₂, semi-inverted.

four patients the T wave became large and pointed (fig 4 A), in fourteen it became low or, more often, inverted. The changes were often progressive, frequently from day to day. In the ten patients who went on to inversion of the T wave, as in the case outlined, a close similarity to the sequence in myocardial infarction could be noted, especially when the T wave was cove-plane, definite RT abnormalities, however, were lacking. The simulation of infarction was enhanced by the fact that the changes occurred in the first and second leads, as in involvement

¹³ Master, A. M. P-Wave Changes in Acute Coronary Artery Occlusion. *Am Heart J* 8:462, 1933.

of the anterior surface of the heart (figs 1, 4 *B* and 5) It should be remembered that other conditions produce similar changes In the majority of patients, however, the changes, though definite, were less characteristic, the T waves in leads I and II, less commonly in the first lead alone, became iso-electric or small (fig 3 *B*) Changes in the T_s wave were usually slight and of doubtful significance, the pointed T_s wave noted by Langendorf and Pick¹⁰ was not observed Regression of the changes was often gradual, requiring one or two weeks for complete disappearance, in some cases the T wave was still small when the

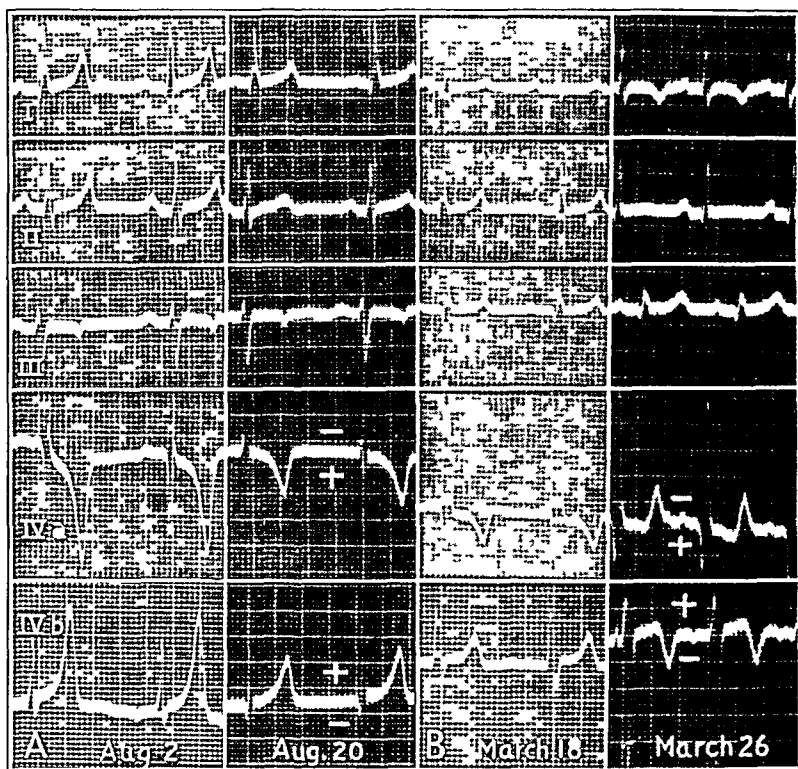


Fig 4—*A*, case 10, a man aged 34 Aug 2 Waves T_1 , T_2 and T_4 , pointed and of high voltage, preponderance of the left ventricle and slurring of the QRS complex, PR interval, twenty-one hundredths to twenty-two hundredths of a second Aug 20 Eighteen days later, T wave of normal voltage, smaller P wave, PR interval, eighteen hundredths of a second *B*, case 13, a man aged 41 March 18 Normal record except for slight slurring of the QRS complex March 26 Wave T_1 , inverted and cove-plane, T_2 , iso-electric, T_4 , of negative polarity

patients were discharged These changes almost always outlasted the clinical symptoms

It is interesting to note that changes frequently occurred also in the precordial lead In our series an abnormal T_4 wave (negative or less than 1 mm) occurred five times, always in association with inversion of the T wave in the standard leads (figs 1, 4 *B* and 5) Another significant change, which was not present in the patients reported on

by Langendorf and Pick,¹⁰ was the absence of the initial positive deflection in three patients (fig 1). Heretofore this finding has been associated by most authors with anterior infarction. Hence the typical electrocardiographic picture of the anterior infarction may be simulated in acute nephritis when waves T_1 and T_2 are inverted, the initial positive deflection is absent and the T_4 wave is of negative polarity. In all three patients absence of the initial positive deflection was transient, in one it became normal, but in the other two it remained small (2 mm or less). In a study to be published¹⁴ it has been shown that an initial positive

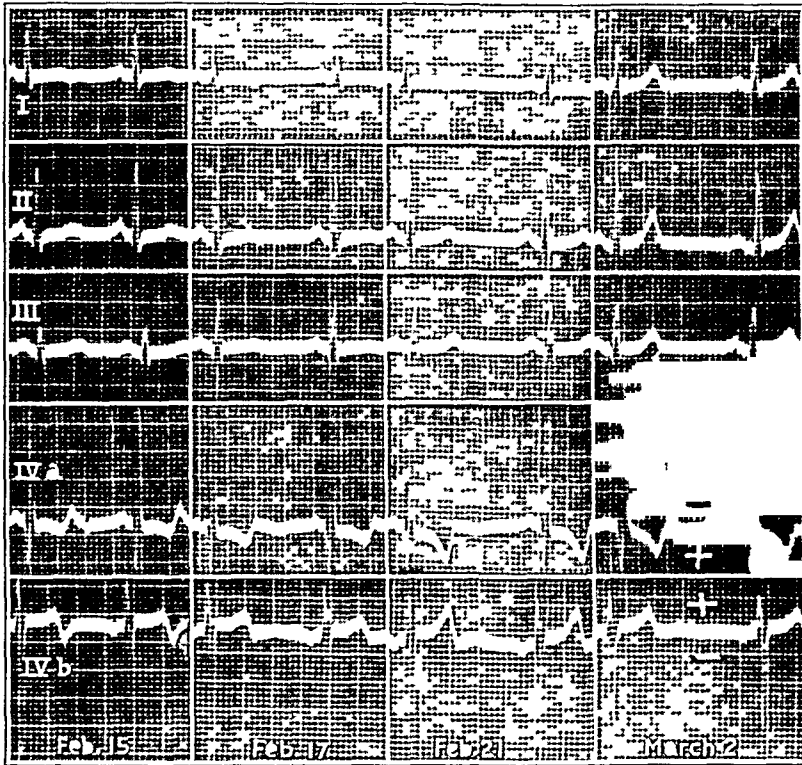


Fig 5 (case 5, a man aged 32)—Feb 15 Wave T_1 , semi-inverted, T_1 , diphasic Feb 17 T_2 , semi-inverted Feb 21 T_2 , upright, T_4 , normal March 2 Normal T wave in all leads

deflection of this size is usually abnormal and that changes in this wave may occur in the absence of infarction.

An attempt was made to correlate the presence of cardiac involvement with changes in the electrocardiogram. This was not always successful, thus two of the eight patients with definite evidence of failure of the left ventricle presented normal electrocardiograms. The remaining six, however, showed striking changes in the T wave and twice the initial positive deflection was absent, in none of these patients was the

14 Master, A. M., Dack, S., Kalter, H., and Jaffe, H. L. The Significance of an Absent or Small Initial Positive Deflection in the Precordial Lead, *Am Heart J* 14: 297, 1937.

PR interval prolonged Nor were the changes in the electrocardiogram always coincident with the presence of hypertension or cardiac insufficiency In the majority of patients they appeared later and remained when the blood pressure had returned to normal It is notable, furthermore, that in one case death occurred after the electrocardiogram had become normal

COMMENT

Hypertension is the rule in acute glomerulonephritis Cardiac insufficiency is common and at times is severe enough to cause death It has usually been assumed that the failure depended directly on the rise in blood pressure and represented the inability of the left ventricle to cope with the sudden increased peripheral resistance This explanation, however, does not seem to hold in most cases In several patients with cardiac failure the blood pressure did not rise much, thus while it reached 200 mm in two instances, the average elevation was only to from 150 to 160 mm Furthermore, this elevation was always temporary, indeed, as we have seen, the blood pressure frequently returned to normal in a week It is unlikely that a heart of normal structure would fail in the presence of such a transient and moderate increase in work Failure does not occur, for example, as a result of the sudden elevation in pressure associated with tumor of the adrenal medulla or with lead poisoning

These clinical considerations lead, therefore, to the conclusion that in acute glomerulonephritis the heart, as well as the kidneys and other organs, is involved in a universal vascular lesion The latter involves the smaller vessels diffusely, giving rise almost uniformly to some increase in blood pressure at the onset of the disease This is independent of renal involvement In many cases, furthermore, the injury to the heart is severe enough to produce profound changes in the electrocardiogram, usually considered indicative of diffuse cardiac damage, including the myocardium (QRS and T waves) and the conduction system (PR interval) The objection may be raised that the inversion of the T wave in leads I and II in our patients was produced by a change in size and shape of the left ventricle consequent to the hypertension and did not represent actual injury to the heart The influence of the configuration of the heart on the electrocardiogram has been stressed¹⁵ Yet this would not account for the prolongation of the PR interval or for the appearance or persistence of the changes after the hypertension and cardiac dilatation have disappeared Hence both the

¹⁵ Master, A M Characteristic Electrocardiograms and Roentgenograms in Arterial Hypertension, *Am Heart J* **5** 291, 1930, Right Ventricular Preponderance (Axis Deviation) of the Heart, *Am J M Sc* **186** 714, 1933 Barnes, A R The Clinical Significance of Certain Abnormalities of the T-Wave in the Electrocardiogram, *Proc Staff Meet, Mayo Clin* **8** 54 (Jan 25) 1930

electrocardiographic abnormalities and the myocardial insufficiency seem to bespeak actual myocardial changes. It was therefore surprising not to observe gross anatomic or significant microscopic changes in routine sections of the hearts of six patients outside of our series as well as in sections of the heart of one patient in our series, who was examined post mortem at this hospital by Dr. Paul Klemperer. Several showed edematous infiltration of the musculature of the heart, in one patient who showed clinical signs of severe failure of the left side of the heart the process was advanced enough to be termed serious myocarditis, for there were, in addition, numerous small foci of infiltration with lymphoid cells. The exact significance of these changes is not certain. However, the usual mechanism of the formation of edema in general is capillary damage, and this may be presumed to hold in these cases, despite the impossibility of demonstrating this change morphologically. It is noteworthy that Stone¹⁶ reported one instance of arteriolitis of the heart in acute nephritis, as well as in other organs in other cases. The absence of visible microscopic changes in the capillaries in these cases does not preclude the possibility of capillary derangement, toxic or chemical in nature. In acute glomerulonephritis there is a profound physiologic alteration of the tissue fluids and electrolytes, as evidenced by edema, which is almost invariably observed in the skin and not infrequently in the brain. It is not unlikely that the internal organs, including the heart, are affected similarly. The myocardial injury which follows accounts for the electrocardiographic changes reported, and if a marked elevation in blood pressure occurs and the damaged heart is unable to cope with the increased work, heart failure ensues.

SUMMARY

Acute glomerulonephritis is sometimes associated with clinical symptoms of failure of the left ventricle, such as, dyspnea, cyanosis and pulmonary edema. These appear early in the course of the disease, in fact, they may be the presenting symptoms and may occur before there is evidence of renal injury. The involvement of the heart is the result of vascular and not renal damage.

The diffuse vascular change also produces hypertension, which is almost always present in the first week or two of the disease.

Changes occur in the electrocardiogram which indicate myocardial damage, that is, definite abnormalities of the T wave in leads I, II and IV, absence of the initial positive deflection in the precordial lead and prolongation of the auriculoventricular conduction time.

Acute glomerulonephritis is a systemic vascular disease in which the heart may be seriously damaged.

¹⁶ Stone, W. J. *Bright's Disease and Arterial Hypertension*, Philadelphia, W. B. Saunders Company, 1936.

RENAL FUNCTION IN OBSTRUCTIVE JAUNDICE

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PHILADELPHIA

Obstructive jaundice produces anatomic changes in the kidneys consisting chiefly of degeneration of the tubular epithelium, long familiar to pathologists under the name cholemic nephrosis. The resulting disturbances in renal function, although recognized by clinicians, have received relatively little recent study. In the present report are given the observations made on a group of patients with obstructive jaundice on whom tests of renal function were employed in an effort to delineate more carefully the clinical features of the renal lesion and to determine the severity and the course. The results indicate that clinically detectable jaundice is invariably associated with the appearance of rather characteristic abnormalities of the urine and frequently with decreased renal function. The evidence of the renal lesion disappears promptly as the jaundice subsides, leaving no detectable sign of residual damage.

METHODS OF STUDY

The subjects of the investigation were sixteen patients suffering from obstructive jaundice and one patient with arsenical hepatitis admitted to the medical or surgical wards of the University Hospital. Only those patients were selected for whom it was possible to rule out preexisting renal disease with reasonable certainty. There were ten males and seven females, their ages ranging from 7 to 74 years. Renal function was tested by the method of Addis¹. Urine was collected for twelve hours, and the formed elements in a measured portion were enumerated. Protein precipitated from a filtered sample of urine by acetic acid was measured gravimetrically. The formed elements and protein excreted in twelve hours were calculated. Urea clearance was determined, the sample of blood being obtained at the end of a twelve hour collection of urine². No attempt was made to determine the concentrating power of the kidneys, since in many cases it seemed inadvisable to restrict the intake of fluid. A quantitative van den Bergh estimation was carried out on the day the renal function was tested.

The expense of this investigation was in large part defrayed by a grant from the Commonwealth Fund.

From the Gastro-Intestinal Section and the Renal Section of the Medical Clinic, the University of Pennsylvania Hospital.

1 Addis, T., and Oliver, J. The Renal Lesion in Bright's Disease, New York, Paul B. Hoeber, Inc., 1931.

2 Landis, E. M., Elsom, K. A., Bott, P. A., and Shiels, E. Observations on Sodium Chloride Restriction and Urea Clearance in Renal Insufficiency, J. Clin. Investigation **14** 525, 1935.

RESULTS

The results are given in the accompanying table. It is apparent that in every patient the urinary sediment was abnormal and that the deviations from normal were qualitatively consistent (chart 1). The outstanding abnormality was the increased excretion of casts, which in some patients were present in enormous numbers. The casts were usually either small and coarsely granular or hyaline, and adherent to them were bile-stained renal epithelial cells. A less striking but equally consistent abnormality was the increased number of epithelial cells and leukocytes, most of which were deeply bile stained. It is believed that

Data for Seventeen Patients

Case	Age	Clinical Diagnosis	Van den Bergh Units	Addis Sediment Count			Blood Urea Nitrogen, Mg per 100 Cc	12 Hour Urea Clearance, % of Normal	Protein Excretion, Mg per 12 Hr	Plasma Protein, Gm per 100 Cc
				Casts, Thousand per 12 Hr	Epithelial and White Blood Cells, Million per 12 Hr	Erythrocytes, Million per 12 Hr				
		Normal		5	2 00	0 50	15 0		100	
1	33	Carcinoma of pancreas	27 0	80	8 00	0 11	6 6	74	0	5 0
2	7	Catarrhal jaundice	24 0	2,224	3 20	0 00	12 8	107	250	9 0
3	72	Cholelithiasis	24 0	457	19 00	0 79	12 4	113	0	
4	62	Carcinoma of liver	21 0	209	3 60	1 30	12 8	68	0	5 7
5	52	Carcinoma of pancreas	24 0	541	2 60	0 48	15 5	48	130	
6	32	Obstruction of common duct	24 0	198	9 00	0 23			400	
7	49	Carcinoma of stomach	20 4	124	7 60	2 30	20 3	48	17	4 5
8	39	Calculous cholecystitis	18 4	205	6 30	0 25	8 2	66	30	
9	32	Arsenical hepatitis	16 0	233	2 80	2 30	5 6	104	30	
10	48	Undetermined	15 0	345	12 30	0 44	8 1	68	0	
11	36	Hepatic cirrhosis	14 4	120	11 00	40 00	18 8	35	0	6 1
12	53	Stenosis of common duct	13 0	49	2 60	0 30	5 4	96	0	6 9
13	46	Carcinoma of gallbladder, metastasis to liver	11 0	302	11 00	2 20	28 1	70	300	5 0
									19	6 7
14	67	Cholelithiasis	7 3	157	17 00	130 00	20 6	30		
15	39	Catarrhal jaundice	4 8	42	2 20	0 90	19 8	57	0	
16	74	Cholecystitis	4 0	11	1 30	0 10	10 0	48	40	
17	56	Calculous cholecystitis	3 7	30	0 94	1 60	16 1	23	20	

they were derived from the renal epithelium and were not simply extra-renal cells stained by the urine in which they were immersed. Some of the epithelial cells contained the pigment granules described by Haessler, Rous and Broun.³ Irregular extracellular particles, which these authors found gave an intense Gmelin reaction, were observed in the sediment. As in the true nephrotic syndrome, the number of red blood cells excreted was conspicuously small. In nine patients the erythrocyte count was within normal limits, in six others it was moderately increased and in only two was it significantly increased. Albuminuria was even less conspicuous. Thirteen of the seventeen patients excreted no more

³ Haessler, F. H., Rous, P., and Broun, G. O. The Renal Elimination of Bilirubin, *J. Exper. Med.* **35** 533, 1922.

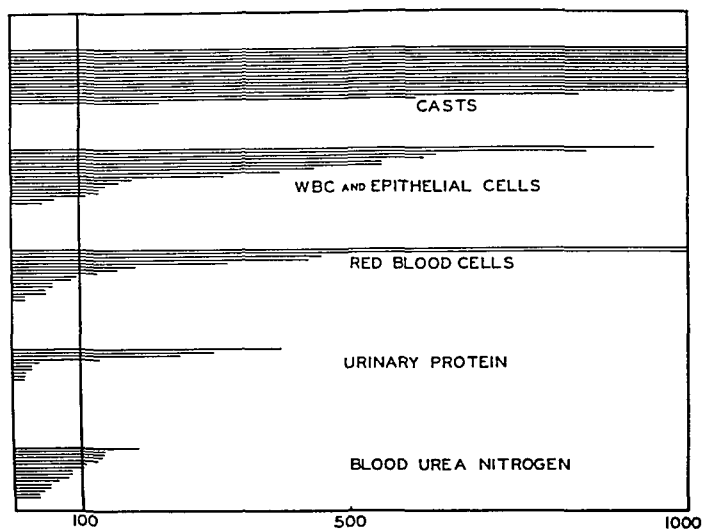


Chart 1—The abnormalities in the urinary sediment. Each line represents the value for a single patient, given in percentage of normal. The greatest number of casts excreted was 44,000 per cent of the normal figure.

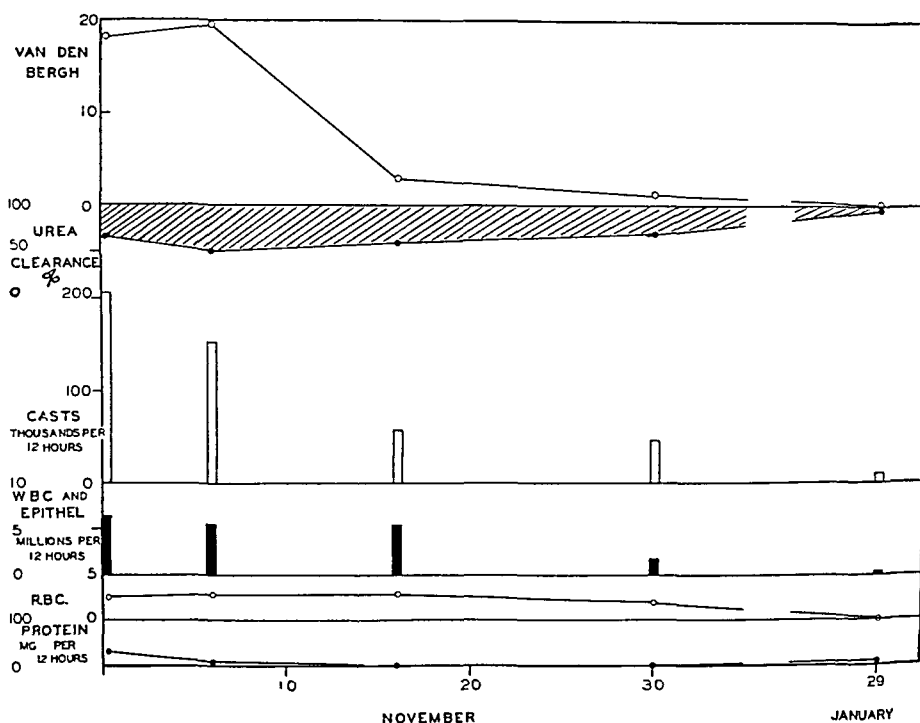


Chart 2—The subsidence of the renal lesion in one patient (case 8)

protein than do normal persons, and the remaining four excreted only slightly more than normal. It is this fact which sharply distinguishes the present disorder from the usual clinical forms of nephrosis, for, as one would anticipate, no one of the patients described here had demonstrable edema or the other clinical features of the nephrotic syndrome. The estimation of the protein content was carried out on a filtered sample of urine, which therefore was free from casts and cells. It is worthy of notice that these elements contribute an amount of protein to the urine which is insignificantly small, judged by an analysis of the urine of the patient (case 2) for whom the highest number of casts was observed. The amount of protein excreted in twelve hours was 267 mg. in unfiltered urine and 250 mg. in filtered urine, a difference almost within the limits of error of measurement in a 10 cc. sample. The value for the urea nitrogen content of the blood was normal in most instances, the highest figure recorded was 28 mg. per hundred cubic centimeters. The urea clearance of the group as a whole was extremely variable, being significantly⁴ decreased in only half the subjects.

Repeated observations of several subjects during recovery from the jaundice yielded data of interest concerning the course of the renal lesion. In each patient the evidence of the renal damage disappeared *pari passu* with the icterus. In one subject (chart 2, case 2) the renal function promptly returned to normal as the jaundice disappeared. Eight weeks after the height of the disease the urinary sediment was entirely normal, and the urea clearance, which had been 50 per cent of normal, had returned to normal.

COMMENT

The term cholemic nephrosis implies that there is renal damage due to some of the constituents of retained bile. The recent demonstration of Stewart and Cantarow⁵ that bile salt (sodium dehydrocholate) may produce in the kidneys of animals degenerative lesions similar to those which constitute the pathologic picture of cholemic nephrosis greatly strengthens this implication. It would be unwarranted on this ground alone, however, to attribute the renal damage solely to the retention of bile, for in biliary obstruction there also occurs damage to the hepatic cells which may result in the production of other nephrotoxic sub-

⁴ Standards for normal have not been fully worked out for the twelve-hour urea clearance without restriction of fluids. In the present study the lower limit has been somewhat arbitrarily set at 80 per cent of normal.

⁵ Stewart, H. L., and Cantarow, A. Renal Lesions Following Injection of Sodium Dehydrocholate in Animals With and Without Biliary Stasis, *Arch Path* 20: 866 (Dec.) 1935.

stances⁶ This is borne out by clinical reports⁷ in which renal insufficiency has occurred in patients with hepatic disease not associated with jaundice In these cases it was assumed that injury to the liver resulted in the elaboration of nephrotoxic substances, probably protein in nature Attempts to produce these substances in animals by reduction of the hepatic blood supply, trauma to the liver and extraction of hepatic tissue by various methods have been partially successful, but the exact nature of the substances so produced is not known⁸ The present study provides no data concerning the relative parts played by various factors presumed to produce the renal damage, such as retained bile salt and hepatic nephrotoxins The fact that three patients who had conspicuous renal damage also showed normal tolerance to galactose inclines one, however, to regard the products of hepatic damage as a less important cause of renal injury than the retained bile, although this must remain a matter of conjecture until more delicate tests of hepatic function are developed

It is of interest to examine the clinical evidence of renal damage in the light of the histologic changes known to occur in the kidneys of jaundiced patients These are degenerative rather than inflammatory, varying in degree from simple cloudy swelling to complete necrosis of the tubular epithelium There is a variable amount of cellular debris, bile pigment and albuminous material in the lumens of the tubules, which are sometimes obstructed and widely dilated The glomeruli, as in other forms of nephrosis, appear to be relatively normal⁹ The presence in the urinary sediment of large numbers of casts, renal epithelial cells and leukocytes and the striking absence of erythrocytes are the findings one would anticipate in a noninflammatory desquamative pathologic process within the kidneys The transient reduction in the urea clearance may be due to the temporary damage to the tubular epithelium, through which an abnormally great back-diffusion of urea occurs, such as is thought to take place in mercury bichloride poisoning The glomeruli, which appear to be anatomically normal, maintain their

6 Lichtman, S S, and Sohval, A R Clinical Disorders with Associated Hepatic and Renal Manifestations, with Special Reference to the So-Called "Hepatorenal Syndrome," *Am J Digest Dis & Nutrition* **4** 26, 1937

7 (a) Helwig, F C, and Schutz, C B A Liver Kidney Syndrome Clinical, Pathological, and Experimental Studies, *Surg, Gynec & Obst* **55** 570, 1932 (b) Fitz-Hugh, T, Jr Hepato-Urologic Syndromes Obstructive Jaundice and Nephritis, *Urologic Infections and Cholemia*, *M Clin North America* **12** 1101, 1929

8 Boyce, F F, and McFetridge, E M So-Called "Liver Death" A Clinical and Experimental Study, *Arch Surg* **31** 105 (July) 1935 Helwig and Schutz^{7a}

9 Wilbur, D L The Renal Glomerulus in Various Forms of Nephrosis, *Arch Path* **18** 157 (Aug) 1934

impermeability to protein, so the reduction of plasma protein that is sometimes observed is not the result of a loss of protein. It should be emphasized that the term cholemic nephrosis is descriptive of the pathologic changes within the kidneys and does not signify the presence of the nephrotic syndrome considered in the clinical sense.

In no one of the patients described here was the disturbance in renal function of serious clinical significance. Nor does it seem likely, in view of the prompt disappearance of all evidence of renal damage, that the kidneys sustained permanent injury which might later become manifest. While in most instances the renal disturbance incident to jaundice is probably a matter of less concern than the underlying disease, it may assume a rôle of dominant importance, particularly if surgical treatment is undertaken. Walters and Parham,¹⁰ Wilbur,⁹ Rowntree¹¹ and Bartlett¹² have described cases in which renal insufficiency followed operations for the relief of biliary obstruction. Of the twenty-one acutely ill, jaundiced patients described by Meyers, Brines and Juliar,¹³ five whose kidneys showed no other pathologic changes than those of cholemic nephrosis had renal failure. In one of Fitz-Hugh's^{7b} patients incipient uremia threatened life but completely disappeared when the jaundice had subsided after cholelithotomy. The disturbance in renal function incident to jaundice may therefore become a matter which greatly influences the practical management of patients with biliary obstruction, hence its degree and course should be carefully assessed.

SUMMARY

Sixteen patients with obstructive jaundice and one patient with arsenical hepatitis presented signs of renal damage, consisting chiefly of excessive excretion of casts, epithelial cells and leukocytes. Hematuria and albuminuria were inconspicuous. The urea clearance was frequently reduced. As the jaundice subsided the evidence of renal injury entirely disappeared.

Miss E. H. Shiels performed the chemical analyses included in this report.

10 Walters, W., and Parham, D. Renal and Hepatic Insufficiency in Obstructive Jaundice, *Surg., Gynec. & Obst.* **35** 605, 1922.

11 Rowntree, L. G. Certain Clinical and Terminal Pictures in Hepatic Disease, *M. Clin. North America* **13** 1399, 1930.

12 Bartlett, W., Jr. Renal Complications of Biliary Tract Infections, *Surg., Gynec. & Obst.* **56** 1080, 1933.

13 Meyers, S. G., Brines, O. A., and Juliar, B. The Acutely Ill, Jaundiced Patient. A Report of Twenty-One Instances of Hepatic Icterus, Seven of Whom Had High Blood Nitrogen, *Am. J. Digest. Dis. & Nutrition* **2** 346, 1935.

CARDIAC OUTPUT IN HEART DISEASE

DETERMINED BY THE DIRECT FICK METHOD, INCLUDING COMPARATIVE DETERMINATIONS BY THE ACETYLENE METHOD

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CINCINNATI

Contradictory results regarding the output of the heart in congestive failure have been obtained by various indirect methods. These results have led to two distinct ideas regarding the relationship of cardiac output to heart failure. 1 The signs and symptoms of cardiac failure are the result of diminished cardiac output—Mackenzie,¹ Lewis,² Meakins and Long,³ Means,⁴ Stewart and Cohn,⁵ Blumgart, Riseman, Davis and Berlin,⁶ and Henderson, Haggard and Dolley.⁷ 2 There is no consistent relationship between cardiac output and heart failure—Harrison⁸ and Hamilton, Moore, Kinsman and Spurling.⁹

From the Department of Internal Medicine, the University of Cincinnati

1 Mackenzie, James. *Diseases of the Heart*, London, H Frowde, 1913

2 Lewis, Thomas. *Diseases of the Heart*, New York, The Macmillan Company, 1933, p 2

3 Meakins, J, and Long, C N H. *Oxygen Consumption, Oxygen Debt and Lactic Acid in Circulatory Failure*, *J Clin Investigation* **4** 273, 1927

4 Means, J H. *Dyspnoea*, *Medicine* **3** 309, 1924

5 Stewart, H J, and Cohn, A E. *Studies on the Effect of the Action of Digitalis on the Output of Blood from the Heart. II. The Effect on the Output of Hearts of Dogs Subject to Artificial Auricular Fibrillation*, *J Clin Investigation* **11** 917, 1932

6 Blumgart, H L, Riseman, J E F, Davis, D, and Berlin, D D. *Therapeutic Effect of Total Ablation of Normal Thyroid on Congestive Heart Failure and Angina Pectoris. III. Early Results in Various Types of Cardiovascular Disease and Coincident Pathologic States Without Clinical or Pathologic Evidence of Thyroid Toxicity*, *Arch Int Med* **52** 165 (Aug) 1933

7 Henderson, Y, Haggard, H W, and Dolley, F S. *The Efficiency of the Heart, and the Significance of Rapid and Slow Pulse Rates*, *Am J Physiol* **82** 512, 1927

8 Harrison, T. *Failure of the Circulation*, Baltimore, Williams & Wilkins Company, 1935, p 69

9 Hamilton, W F, Moore, J W, Kinsman, J M, and Spurling, R G. *Studies on the Circulation. Further Analysis of Injection Method, and of Changes in Hemodynamics Under Physiological and Pathological Conditions*, *Am J Physiol* **99** 534, 1932

The results of indirect methods have been adversely criticized because different methods have given widely varying values. Even the original acetylene method of Grollman,¹⁰ which is generally considered the best of the indirect methods, has been modified by its originator when used for patients with congestive heart failure, as pulmonary congestion and sluggish blood flow greatly impair its reliability.

It seems that a proper evaluation of the acetylene method as modified for use in patients with congestive failure can be determined only by application of the direct Fick method,¹¹ which Grollman has said "is so direct and unequivocal that the results are open to no possible cavil." We have therefore compared the cardiac output by the direct and the three-sample acetylene method and have in addition studied the cardiodynamics of these patients in order to establish so far as possible the degree of failure of the right and left ventricles in each.

Only three patients with myocardial insufficiency have previously been studied by the direct Fick method. This study was carried out in 1930 by Baumann, Lauter¹² and Friedlander, who reported subnormal values in three cases of cardiac asthma, i. e., 2.3, 3.1 and 3.3 liters per minute. Unfortunately no clinical data concerning the character of the heart disease or the severity of the cardiac asthma in these three patients were included in their report. Shortly thereafter Baumann¹³ studied ten normal persons by the direct method and found that the cardiac output ranged between 5.1 and 4.3 liters per minute, the average output being 4.6 liters. Baumann and Grollman¹⁴ employed the direct Fick method in studying patients without evidence of heart disease and compared the results with values obtained by the two-sample acetylene method. A considerable variation in the output of the heart was demon-

10 Grollman, A. *The Cardiac Output of Man in Health and Disease*, Springfield, Ill., Charles C. Thomas, Publisher, 1932, p. 206. The rather complicated technic of this method is described in detail by Grollman. The cardiac output is determined by obtaining the oxygen consumption and the arteriovenous oxygen difference.

11 It was first pointed out by Fick in 1870 that the output of the heart can be determined if the following facts are known: (1) oxygen content of the mixed venous blood, (2) oxygen content of the arterial blood and (3) oxygen consumption per minute, e. g., (1) oxygen content of mixed venous blood = 15 volumes per cent, (2) oxygen content of arterial blood = 19 volumes per cent and (3) oxygen consumption per minute = 200 cc. The blood flow through the lungs = $\frac{100}{4} \times 200 = 5$ liters per minute.

12 Lauter, S. *Kreislaufprobleme*, München med. Wchnschr. **77** 526 (March 28), 593 (April 4) 1930.

13 Baumann, H. *Ueber die wahre Grosse des Minutenvolumens*, Verhandl. d. deutsch. Gesellsch. f. inn. Med. **42** 248, 1930.

14 Baumann, H., and Grollman, A. *Ueber die theoretischen und praktischen Grundlagen und die klinische Zuverlässigkeit der Acetylenmethode zur Bestimmung des Minutenvolumens*, Ztschr. f. klin. Med. **115** 41, 1930.

strated, the values ranging from 3.1 to 11.8 liters per minute, but remarkably close agreement was secured when the same patients were examined with the acetylene method. The average cardiac output by the direct method was 6.1 liters per minute and by the acetylene method 6 liters per minute.

In 1930 Klein¹⁵ employed the direct Fick method in man, securing blood from the right side of the heart by introducing a catheter into the right auricle through an antecubital vein. In one normal patient the cardiac output was 4.4 and in a second patient 4.2 liters per minute.

METHOD

For the persons studied by us the determinations were made under basal conditions. The analyses of blood were carried out according to the method and with the apparatus of Van Slyke¹⁶.

The direct Fick procedure was carried out according to the technic described by Grollman¹⁰. Arterial puncture was made after collection of mixed venous blood Grollman's acetylene method, as modified by Grollman and his colleagues¹⁷ to measure the cardiac output of patients with congestive failure, was carried out within forty-eight hours of the time of the direct determination, except for the sixth patient, in this case twenty-eight days elapsed between the determinations. As the clinical condition of this patient remained essentially unchanged, the data regarding the cardiac output are included.

Neither immediate reactions nor subsequent complications were associated with this investigation, but because of theoretical hazards, such as injury to an important coronary vessel or the establishment of serious arrhythmia, we have decided to make no further studies necessitating direct determinations by the Fick method.

For two of the patients studied the diagnosis of pericardial effusion had been made by means of roentgenograms, and the collection of mixed venous blood was a diagnostic procedure. In the other cases permission for the collection of samples was obtained from the patients, who, although suffering from hopeless disease, had become accustomed to painless collection of samples of blood after careful infiltration of the skin with procaine hydrochloride even for simple venous punctures.

For half the patients the direct method preceded the determination by the acetylene method, while the procedure was reversed for the remaining patients. As the relationship between the acetylene and the direct method was consistent, no apparent error was introduced. Acetylene determinations for normal persons were carried out at various times to check the accuracy of our technic. The output for these persons averaged 2.2 liters per square meter of body surface, a value considered by Grollman to be normal.

15 Klein, O. Zur Bestimmung des zirkulatorischen Minutenvolumens beim Menschen nach dem Fickschen Prinzip, *München med Wchnschr* **77** 1311 (Aug 1) 1930.

16 Peters, J. P., and Van Slyke, D. D. *Quantitative Clinical Chemistry* Baltimore, Williams & Wilkins Company, 1932, vol 2, p 324.

17 Grollman, A., Friedman, B., Clark, G., and Harrison, T. R. *Studies in Congestive Heart Failure XXIII. A Critical Study of Methods for Determining the Cardiac Output in Patients with Cardiac Disease*, *J Clin Investigation* **12** 751, 1933.

COMMENT

Brief abstracts of the records of the patients studied will be presented to illustrate the clinical condition of each patient

The degree of cardiac insufficiency in each patient at the time of the determinations can best be evaluated by examining the accompanying table, where in the majority of cases vital capacity, venous pressure, cardiac size in relationship to thoracic diameter, arterial blood pressure and velocity of blood flow are reported. For all the patients save one (case 2) admission to the hospital was urgently necessitated because of symptoms and signs of myocardial insufficiency, in fact, all except the second and fourth patients had been repeatedly admitted to the hospital because of congestive failure. However, at the time of the determinations of the cardiac output varying degrees of improvement in symptoms and physical findings had resulted from rest, the administration of digitalis and other therapeutic procedures. Consequently the status of cardiac efficiency at the time of the determinations of cardiac output can best be evaluated by a consideration of the measurements of circulatory functions of each patient

CASE 1—Rheumatic heart disease, mitral insufficiency mitral stenosis, aortic insufficiency and possibly tricuspid insufficiency

H D, a 58 year old night-watchman, was admitted to the hospital for the fifth time, complaining of effort dyspnea of three years' standing, recent precordial pain and edema of the ankles. Physical examination at the time of the determination of the cardiac output showed moderate dyspnea at rest and slight engorgement of the cervical veins. The blood pressure was 122 systolic and 82 diastolic. The pulse was completely irregular, the rate being 50. (An electrocardiogram showed auricular fibrillation, with low voltage of QRS in all leads.) The heart was 19 cm in diameter in the teleroentgenogram, with obliteration of the waistline. There was a loud systolic and a softer mid-diastolic murmur at the cardiac apex. There was also a soft diastolic murmur at the aortic area. Small amounts of fluid were noted at the bases of the lungs, but no râles were heard over this area. The liver extended 4 fingerbreadths below the costal margin and pulsated during systole. Ascites and moderate edema of the ankles were present. The vital capacity was 75 per cent of normal. The Wassermann reaction was negative. There were 4,600,000 erythrocytes and the hemoglobin content was 65 per cent (Sahli). Urinalysis revealed no abnormality except 1+ albumin and occasional casts.

The cardiac output as determined by the direct method was 1.79 liters per square meter, or 3.02 liters per minute. The output by the acetylene method was 1.31 liters per square meter, or 2.19 liters per minute.

CASE 2—Rheumatic heart disease, mitral stenosis and insufficiency and subacute bacterial endocarditis

B H, a 42 year old woman, was admitted to the medical service complaining of weakness, shortness of breath and "rheumatism." She had chorea when 9 and 13 years old and migratory polyarthritides six months before admission to the hospital. Recently she had been troubled with chills, fever and shortness of breath. The temperature was 101 F, the pulse rate 90 and the blood pressure 100 systolic and 90 diastolic. Petechiae were scattered over the neck. The heart was enlarged

Data for Six Patients

Case No	Initials	Sex	Age	Etiology of Heart Disease	Cardiac Rate	Rhythm	Diameter of Heart, Cm	Diameter of Chest, Cm	Degree of Congestive Failure	Arterial Blood Pressure, Mm of Mercury	Venous Pressure, Cm of Water	Vital Capacity, % of Normal	Metabolic Rate, %	Cardiac Output, Direct Method (Fick)					Cardiac Output by Sample Acetylene Method (Grollman)		
														Liters per Sq M Min	Liters per (Fick), per Sq M Min	Liters per (Fick), per Sq M Min	Liters per (Fick), per Sq M Min	Liters per (Fick), per Sq M Min	Oxygen Capacity, Vol %	Oxygen Capacity, Vol %	Oxygen Capacity, Vol %
1	H D	M	58	Rheumatic heart disease	77	Auricular fibrillation	19	31	++	100/84	8.5+	74	+10	1.79	3.02	39	1.31	2.19	22.3		
2	B H	F	42	Subacute bacterial endocarditis, rheumatic heart disease	92	Sinus	17	27	0	100/78	6.1+	85	+26	2.45	3.60	39	1.91	2.81	13.4		
3	M B	F	75	Arterio sclerosis, hypertensive heart disease	60	Nodal	19	26	+++	190/100	20.0+	40	+19	2.27	3.77	63	1.69	2.82	20.4		
4	W P	M	49	Hypertension	106	Sinus	20	32	+	165/130		60	+11	2.04	3.63	34	2.06	3.57			
5	L A	M	46	Syphilitic heart disease	74	Sinus	27	30	++	150/68	8.8	53	+11	1.56	2.50	34	1.65	2.64	15.7		
6	M T	F	27	Tuberculous pericarditis dilatation hypertrophy	88	Sinus	18	29	++	110/74	20.0+	40	+21	2.04	2.69	31	1.28	1.62			

in all directions, measuring 17 cm in its maximum diameter, the thoracic width was 27 cm. At the apex there was a presystolic thrill, the first sound was snapping and there was a rumbling diastolic murmur with presystolic accentuation. The lungs were clear. The fingers and toes were slightly clubbed. The spleen was palpable. There were 3,600,000 erythrocytes, and the hemoglobin value was 53 per cent. Urinalysis showed 1+ albumin and a few red blood cells on several occasions. Culture of the blood showed *Streptococcus viridans*.

By the direct method the cardiac output was found to be 2.45 liters per square meter of body surface, or 3.6 liters per minute. By the acetylene method the cardiac output was 1.91 liters per square meter of body surface, or 2.81 liters per minute.

CASE 3—Generalized arteriosclerosis, hypertension, cardiac hypertrophy and dilatation and possibly cor pulmonale

M. B., a 75 year old woman, was admitted to the hospital with the complaint of "high blood pressure," effort dyspnea, paroxysmal nocturnal dyspnea and palpitation of the heart. Examination showed the patient to be orthopneic. The lips and nail beds were markedly cyanotic. The blood pressure was 190 systolic and 90 diastolic. The pulse rate was 60, and the beat was regular but with definite pulsus alternans. (The electrocardiogram showed nodal rhythm of type II, with a "coronary" T wave in lead I.) The heart was greatly enlarged, as proved by the teleoroentgenogram. The right ventricle and conus pulmonalis showed definite enlargement. At the apex a gallop rhythm and a systolic murmur were heard. At the bases of the lungs there were numerous râles. Moderate ascites and pitting edema of the legs and skin extending to the twelfth dorsal spine were noted. The peripheral arteries were tortuous and sclerotic. The Wassermann reaction was negative. Urinalysis showed a specific gravity of 1.015 and a trace of albumin. There were 4,400,000 erythrocytes, and the hemoglobin value was 80 per cent (Sahli).

The cardiac output was 3.77 liters per minute by the direct method, or 2.27 liters per square meter of body surface. By the acetylene method the cardiac output was 2.82 liters per minute, or 1.69 liters per square meter of body surface¹⁸.

CASE 4—Arteriosclerotic heart disease, with hypertension and myocardial insufficiency

W. P., a salesman aged 49, had symptoms beginning seven months before his admission to the hospital with effort dyspnea. For two weeks he had had attacks of paroxysmal nocturnal dyspnea and slight edema of the ankles. Five years previously he was told that his blood pressure was "high." At the time of the present examination he was neither dyspneic nor cyanotic. The blood pressure was 150 systolic and 120 diastolic. The heart was 20 cm in diameter, as measured by a teleoroentgenogram. The rhythm was regular. A presystolic gallop rhythm and a systolic murmur were heard at the cardiac apex. The physical signs of fluid in the right side of the thorax were present, and these findings were corroborated by roentgenograms of the chest. Slight pitting edema over the sacrum and moderate edema of both ankles were noted. An electrocardiogram showed inverted T waves in lead I and iso-electric T waves in lead III. There were 4,100,000 erythrocytes, and the hemoglobin value was 78 per cent (Sahli). Urinalysis showed a trace of albumin.

¹⁸ Since the completion of these studies this patient has returned to the hospital in profound congestive failure, with anasarca, deep cyanosis and pulmonary edema. However, the cardiac output by the acetylene method was 2.6 liters per minute twenty-four hours before death.

The cardiac output was 2.04 liters per square meter, or 3.63 liters per minute, by the direct method. The acetylene method showed an output of 2.06 liters per square meter of body surface, or 3.57 liters per minute. Five months later, when the patient was symptom free, the cardiac output by the acetylene method was 3.62 liters per minute.

CASE 5—*Syphilitic aortitis, aortic insufficiency and myocardial insufficiency*

L. A., a Negro aged 46, had had a primary syphilitic lesion twenty-four years before admission to the hospital. He complained of shortness of breath and precordial pain. Effort dyspnea as well as paroxysmal nocturnal dyspnea had been present for two years. Recently edema of the ankles and precordial pain had forced him to bed. When studied by us the pulse rate was 100, regular and Corrigan in character. The blood pressure was 155 systolic and 60 diastolic. The heart was greatly enlarged, measuring 27 cm. To and fro murmurs characteristic of aortic insufficiency were heard at the base of the heart. The lungs were clear. The abdomen showed no abnormalities. There was slight edema of the ankles. The Kahn reaction was 3+. There were 5,000,000 erythrocytes, and the hemoglobin value was 90 per cent (Sahli). The urine contained 3+ albumin and a few leukocytes but no casts.

By the direct method the cardiac output was 1.56 liters per square meter of body surface, or 2.5 liters per minute. The acetylene method gave a value of 1.65 liters per square meter, or 2.64 liters per minute. Five months later, when the patient's condition was definitely improved clinically, the cardiac output was 3.25 liters per minute by the acetylene method.

CASE 6—*Tuberculous polyserositis, cardiac hypertrophy (slight) and dilatation (marked) and cirrhosis of the liver*

M. T., a woman aged 27, had been engaged in housework. On April 1935 she became short of breath and noticed irregularity of the heart, which she thought followed a "cold" in February. She had a history of syphilis, with a positive Wassermann reaction and had received antisyphilitic treatment during the year preceding her entry into the hospital. She complained of "gas on the stomach" and nausea.

Physical examination showed enlargement of the heart, with a "roaring" systolic murmur at the apex. The blood pressure was 120 systolic and 80 diastolic. Ascites and enlargement of the liver and spleen were likewise noted. The legs were moderately edematous. The diagnosis of rheumatic heart disease was made.

After digitalization and the use of mercurial diuretic and paracentesis of the abdomen and chest the patient was discharged. Subsequently she was repeatedly readmitted for thoracic and abdominal paracentesis. On several occasions bloody fluid was obtained. Injection of this fluid into guinea-pigs did not cause the development of tuberculosis. On several of the various admissions to the hospital the patient had fever. A diastolic murmur at the apex of the heart and systolic pulsations in the jugular veins were noted. Transient auricular fibrillation was demonstrated by the electrocardiogram. A roentgenogram showed cardiac enlargement. The fluoroscopic diagnosis was rheumatic heart disease or pericarditis. There were 4,300,000 erythrocytes, and the hemoglobin value was 60 per cent. The Kahn reaction was negative.

The cardiac output by the direct method was 2.04 liters per square meter, or 2.69 liters per minute. By the acetylene method the cardiac output was 1.28 liters per square meter of body surface, or 1.62 liters per minute.

The patient died six months later after repeated readmissions to the hospital, and at autopsy tuberculous polyserositis was noted. The heart was slightly hyper-

trophied, weighing 400 Gm. It was moderately dilated, with an organized mural thrombus of the left auricle. The cardiac valves were normal. The pericardium was thickened, and the visceral and parietal layers were bound together by fibinous adhesions. There were no important external adhesions save those to the pleurae.

CONCLUSIONS

As shown in the protocols and table, a close qualitative comparison between the acetylene and the direct method was demonstrated. The results in two patients (cases 4 and 5) were nearly identical. In the other patients, although the acetylene method gave lower values than did the direct method, the relationship was consistent, in that a low output, as measured by the acetylene method, was likewise low with the direct method. This close relative parallelism was shown in every instance and serves to demonstrate the value of the modified acetylene method in the study of patients with serious heart disease.

No correlation between the level of cardiac output and the degree of circulatory inefficiency as measured by the velocity of blood flow, the venous pressure or the vital capacity, was observed. In other words, one cannot say that the lower the cardiac output, the sicker the patient. In fact, the patient (case 3) who had the largest cardiac output of any of the patients studied unquestionably presented the severest manifestations of congestive failure. This result lends weight to the contention of Harrison that no consistent relationship exists between the degree of failure and the cardiac output. Additional support for this belief is afforded by the measurement of the cardiac output of a patient with complete heart block who exhibited neither symptoms nor signs of cardiac failure and who was studied by Baumann and Lauter¹² with the direct method. The cardiac output was only 2.7 liters per minute, a value lower than those for two of three patients suffering with cardiac asthma who were examined by the same investigator. However, the necessarily small group of patients examined suggests that patients with severe myocardial disease have a subnormal cardiac output even though congestive failure may not be present. In none of the patients was the output as great as normal, either with the acetylene or the direct method. In fact, the output as measured by the direct method gave an average value of 30 per cent below the average normal of 4.6 liters per minute, as reported by Baumann.¹³ Unfortunately this investigator failed to express the cardiac output in terms of liters per square meter of body surface, which undoubtedly would have afforded a superior basis for comparison.

SUMMARY

The cardiac output has been determined by the direct method of Fick and the modified acetylene method of Grollman for six patients

with serious heart disease In all the patients the cardiac output was subnormal

The results demonstrated close qualitative comparison between the modified acetylene and the direct method, although the absolute values tended to be lower by the acetylene method

No relationship between the severity of symptoms or the severity of failure, as judged by measurements of circulatory efficiency, and the level of cardiac output was demonstrated

SUBACUTE COR PULMONALE

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AND

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At present two types of cor pulmonale are recognized—acute and chronic. The former is practically always the result of a single cause, pulmonary embolism, for a clearer understanding of its clinical manifestation one is indebted to the recent writings of Sylvester McGinn and Paul D White¹. In this form, except in those relatively rare instances in which the patient survives repeated attacks over a long period (two months or longer), there is rarely significant hypertrophy of the right ventricle, since the condition either is rapidly fatal or quickly results in complete recovery.

The chronic type of cor pulmonale is of manifold etiology. The most important causes of primary chronic cor pulmonale are mitral stenosis, extensive pulmonary fibrosis and marked emphysema secondary to asthma, chronic bronchitis or some other pulmonary disease. In 14 per cent of a series of one hundred patients with heart failure White² noted primary strain of the right side of the heart due to the aforementioned causes. However, in most of the 74 per cent of the patients in whom there was primary strain of the left ventricle the right chamber was secondarily involved. More recently Thompson and White³ confirmed White's previous observations by a study of seven hundred and four patients with hypertrophy of the right ventricle. In 61 per cent the strain of the right side of the heart was apparently secondary to failure of the left ventricle, since the causes of cardiac strain in this group were arterial hypertension, aortic valvular disease and infarcts of the left ventricle, with no factors demonstrable which might produce primary strain of the right ventricle.

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1 McGinn, Sylvester, and White, Paul D. Acute Cor Pulmonale Resulting from Pulmonary Embolism, *J A M A* **104** 1473-1480 (April 27) 1935. White, Paul D. The Acute Cor Pulmonale, *Ann Int Med* **9** 115-122 (Aug) 1935.

2 White, Paul D. Weakness and Failure of the Left Ventricle Without Failure of the Right Ventricle, *J A M A* **100** 1993-1998 (June 24) 1933.

3 Thompson, W P, and White, Paul D. The Commonest Cause of Hypertrophy of the Right Ventricle—Left Ventricular Strain and Failure, *Am Heart J* **12** 641-649 (Dec) 1936.

Relatively less frequent causes of chronic cor pulmonale are marked deformity of the chest (kyphoscoliosis), certain congenital cardiac lesions, namely, defects of the pulmonary valve, patent ductus arteriosus and septal defects, and rarely organic tricuspid regurgitation

Chronic infiltrative pulmonary lesions (neoplasms, tuberculosis and other chronic inflammatory processes) involving large portions of the pulmonary tissues often cause strain of the right side of the heart, but in these instances (except when extensive fibrosis or marked emphysema develops) the primary disease usually dominates the clinical picture and causes death before the more serious symptoms of strain of the right side of the heart become apparent

Pulmonary arteriosclerosis is commonly associated with sustained increased tension in the pulmonary circulation, and the pulmonary vascular changes and the strain of the right side of the heart are usually the simultaneous results of common etiologic factors. According to Moschcowitz,⁴ "primary arteriosclerosis of the pulmonary vessels, if it exists at all, is extremely rare." However, instances of extensive pulmonary arteriosclerosis without demonstrable causative factors have been reported by Atkins,⁵ Darley and Doan,⁶ Pund and Phinzy,⁷ Ulrich,⁸ Brenner,⁹ Krutzsch¹⁰ and others. For many of these patients there was a history or evidence of pulmonary infection (such as tuberculosis pneumonia or syphilis) sometime prior to the onset of the symptoms of pulmonary arteriosclerosis. Although in most instances the infection had cleared up without significant residua (as determined by clinical and roentgenographic examination or at necropsy), it is possible that during the active stage of the infection sufficient damage had resulted to pulmonary vessels to initiate a sclerosing process which gradually produced narrowing of the pulmonary vascular bed. Congenital anomalies and faulty development have also been suggested as possible

4 Moschcowitz, Eli. Hypertension of the Pulmonary Circulation, *Am J M Sc* **174** 388-405 (Sept) 1927

5 Atkins, H J B. Ayerza's Disease, *Guy's Hosp Rep* **82** 480-489 (Oct) 1932

6 Darley, Ward, and Doan, Charles A. Primary Pulmonary Arteriosclerosis with Polycythemia, Associated with the Chronic Ingestion of Abnormally Large Quantities of Sodium Chlorid (Halophagia), *Am J M Sc* **191** 633-647 (May) 1936

7 Pund, E R, and Phinzy, T B. Primary Sclerosis of the Pulmonary Artery, *Ann Int Med* **5** 1391-1396 (May) 1932

8 Ulrich, H L. The Clinical Diagnosis of Pulmonary Arteriosclerosis, *Ann Int Med* **6** 632-644 (Nov) 1932

9 Brenner, O. Pathology of the Vessels of the Pulmonary Circulation, *Arch Int Med* **56** 978-1014 (Nov) 1935

10 Krutzsch, Gunther. Ueber rechtsseitige Herzhypertrophie durch Einengung des Gesamtquerschnittes der kleineren und kleinsten Lungenarterien, *Frankfurt Ztschr f Path* **23** 247-271, 1920

etiologic factors.⁷ It is clear, therefore, that in the light of present knowledge the possibility must be recognized that "primary" pulmonary arteriosclerosis (degenerative, toxic, infectious or developmental) may be the cause of pulmonary hypertension, with consequent strain of the right side of the heart. The term "primary" is used here not in the sense of "essential" but to denote that the vascular changes preceded the hypertrophy of the right ventricle and may therefore be considered the probable cause of the hypertrophy.

Ayerza's disease is probably best regarded as a syndrome including pulmonary hypertension, pulmonary arteriosclerosis, polycythemia, cyanosis, headache, mental confusion and somnolence, hemoptysis, strain of the right side of the heart and, in the latter stages, the symptoms of failure of the right side of the heart, with congestion. Often bronchitis and cough precede by months or years the onset of the other symptoms and may therefore be of etiologic significance. Syphilis has been claimed as the cause of Ayerza's disease (Arrillaga,¹¹ Escudero¹² and Rogers¹³). Although syphilis was found in about half the patients reported on, "in only one of these was there acceptable evidence that the pulmonary arterial lesions were due to syphilis" (Brenner⁹), and since many instances of typical involvement have been reported in which syphilis was definitely excluded (Atkins,⁵ Brenner⁹ and Hare and Ross¹⁴), the concept that the Ayerza symptom complex is a specific disease of syphilitic origin must be abandoned. This syndrome probably may develop from any lesion that causes hypertension and arteriosclerosis of the pulmonary circulation (Moschcowitz,⁴ Atkins,⁵ Waring and Yegge¹⁵ and others). They are essentially the same factors already described (including syphilitic pulmonary disease), and their relationship to strain of the right side of the heart has already been discussed.

Recently Yater and Hansmann¹⁶ suggested sickle cell anemia as "a new cause of cor pulmonale" and reported on two patients in illustration. In both patients hypertrophy and failure of the right side of the heart

11 Arrillaga, F. C. Sclerose de l'artere pulmonaire, *Bull. et mem. Soc. med. d'hop. de Paris* **48** 292, 1924, cited by Brenner⁹.

12 Escudero, P. Les cardiaques noirs et la maladie de Ayerza, *Arch. d. mal. du cœur* **19** 439, 1926, cited by Brenner⁹.

13 Rogers, L. Extensive Atheroma and Dilatation of the Pulmonary Arteries, Without Marked Valvular Lesions, as a Not Very Rare Cause of Fatal Cardiac Disease in Bengal, *Quart. J. Med.* **2** 1-17 (Oct.) 1908.

14 Hare, D. C., and Ross, J. M. Syphilitic Disease of the Pulmonary Arteries, *Lancet* **2** 808-812 (Oct. 19) 1929.

15 Waring, J. J., and Yegge, W. B. Polycythemia in Association with Pulmonary Disorders, *Ann. Int. Med.* **7** 190-207 (Aug.) 1933.

16 Yater, W. M., and Hansmann, G. H. Sickle-Cell Anemia. A New Cause of Cor Pulmonale, *Am. J. M. Sc.* **191** 474-484 (April) 1936.

were present. The lesions in one patient were thrombotic occlusions of the small and medium-sized arteries of the lungs, in the other there was thickening of the walls of the small and medium-sized arteries and arterioles of the lungs, with narrowing of their lumens, but thromboses were not observed in the tissue studied. The authors suggested that "right heart failure must be common in cases of sickle cell anemia, since many of the patients have enlarged hearts, systolic murmurs, and hepatomegaly."

It is our purpose in this paper to call attention to a clinicopathologic condition producing "subacute" cor pulmonale. This condition, although admittedly rare, is possessed of sufficiently distinguishing features to suggest the possibility of clinical recognition.

REPORT OF A CASE

A married woman aged 36 entered St Vincent's Hospital because of anemia and uterine bleeding. The only significant statement in her previous history was in reference to some vague gastro-intestinal discomfort of about one year's duration, which she desired to have investigated after the anemia and bleeding were controlled. Otherwise her personal and family records were essentially irrelevant. A diagnosis of uterine myofibromas and secondary anemia was made, and after the giving of a blood transfusion supravaginal hysterectomy was performed. The postoperative course was complicated by the development of a pelvic abscess, which was responsible for the temperature ranging from 100 to 103 F. However, except on three days the temperature remained below 101 F, and it appears fair to state that the pelvic infection was a relatively unimportant factor in the production of the major symptoms and in the final outcome. About one week after the operation the patient complained of cough and difficulty in breathing. These symptoms became increasingly pronounced and failed to respond to any of the usual therapeutic measures. Prior to that there had been nothing in the history or examination to suggest any abnormality of the cardiovascular or respiratory systems.

One week after the appearance of dyspnea and cough (fourteenth postoperative day) the condition of the patient became suddenly alarming. The pulse rate, which had been about 100 per minute, increased to 120 per minute. The respirations, which had been about 30 per minute, mounted to 40 per minute, and the temperature dropped to 97 F. The heart action appeared "toxic," the pulse was weak and the blood pressure was 90 systolic and 60 diastolic. Systolic murmurs were heard over the "right ventricle" (lower portion of the sternum) and at the pulmonic area. There was "a very soft murmur at the aortic area." The lungs appeared clear. The liver was just palpable below the costal margin, the spleen was not enlarged. A roentgenogram showed marked dilatation of the second arch of the left cardiac border (indicating enlargement of the pulmonary artery and conus) and considerable perivascular infiltration, which radiated from both hilar areas into the pulmonary fields. There was evidence of some passive congestion. The blood showed moderate anemia (hemoglobin, 70 per cent, red blood cells, 3,480,000).

These symptoms continued for about forty-eight hours. Gradually the pulse grew weaker and finally became imperceptible. Breathing continued for several minutes after the heart had completely stopped. Cyanosis was not marked until shortly before death.

Clinical Diagnosis—Before the information obtained at necropsy was available it was recognized that this was a "cardiac" death in which the inadequacy of the right side of the heart played a prominent part. However, neither the nature of this inadequacy nor its pathogenesis was understood. Because of the fever and "murmurs," the presence of endocarditis was suspected at one time but was not regarded as very probable. There was no history of rheumatism or any other condition that might produce heart disease, and physical examination when the patient was admitted to the hospital revealed no evidence of cardiac or pulmonary involvement. The sudden appearance of dyspnea and cough, together with the

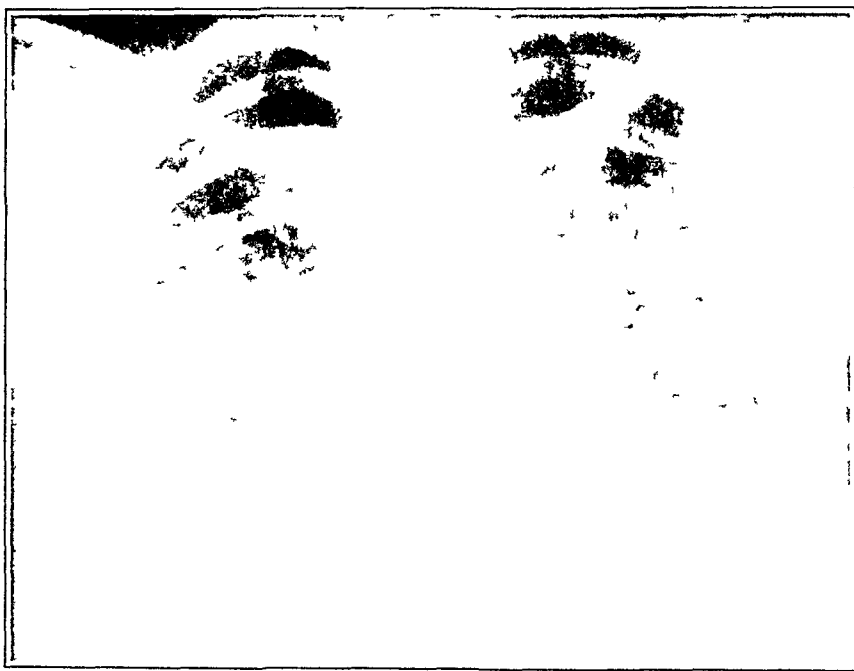


Fig 1—Roentgenogram taken forty-eight hours before death, showing marked dilatation of the pulmonary artery and conus

discovery of roentgenographic evidence of strain of the right side of the heart (dilatation of the pulmonary conus), might have suggested the possibility of pulmonary embolism. However, the absence of pain in the chest, hemoptysis and signs of consolidation would have spoken against this diagnosis. The symptoms of shock were also absent at the onset of the cough and dyspnea, although they did develop one week later and persisted during the last two days of life.

Gross Postmortem Examination—Autopsy was limited to an abdominal incision. The body was that of a well developed and well nourished but rather pale woman. A surgical incision was present in the lower middle portion of the abdomen. It was healing and showed no gross evidence of infection. There was no edema of the extremities or genitalia. A pelvic abscess, located over the cervical stump, contained only a few cubic centimeters of pus. A loop of small intestine was adherent to this site. No free fluid or exudate was present in the abdominal cavity.

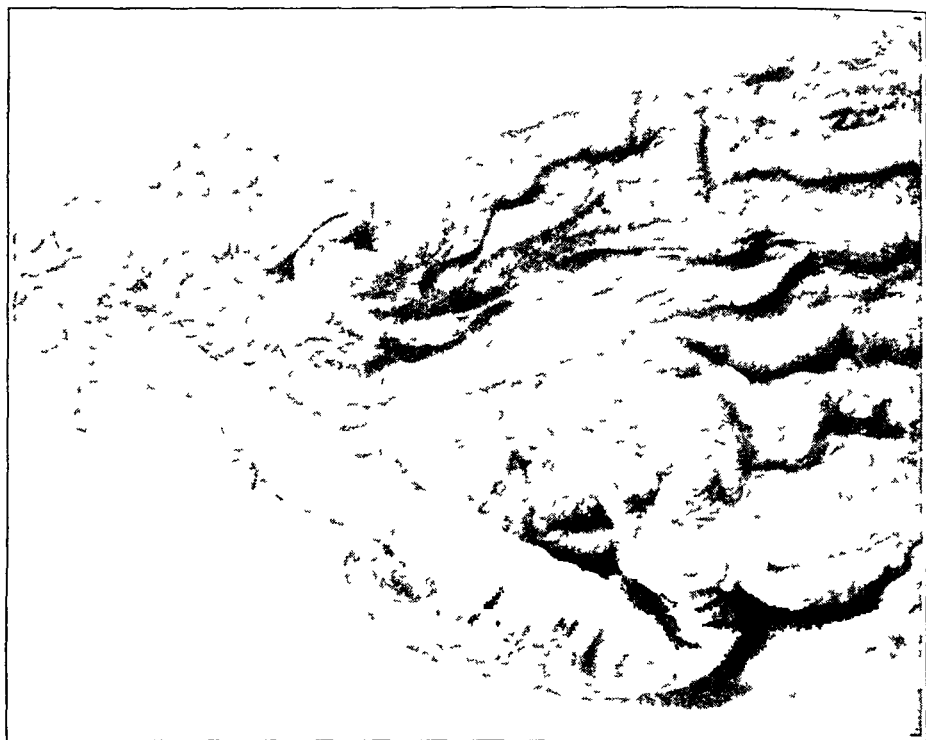


Fig 2—Photograph showing the carcinomatous ulcer of the stomach cut through longitudinally. Note the fibrous streaking of the wall associated with the desmoplastic carcinoma.



Fig 3—Photograph showing enlargement of the trabeculae carneae and papillary muscles and thickening of the wall of the right ventricle.

The liver weighed 1,420 Gm and exhibited a smooth capsule with a sharp inferior edge. The surfaces made by sectioning were rather pale, and the parenchyma was friable.

The external aspect of the stomach was unchanged. When the organ was opened, however, the mucosa was seen to be thickened and presented a morocco leather-like roughening on its surface. It was rugose, except for an area, measuring 2.5 by 1.5 cm, in the lesser curvature, near the pylorus, where the

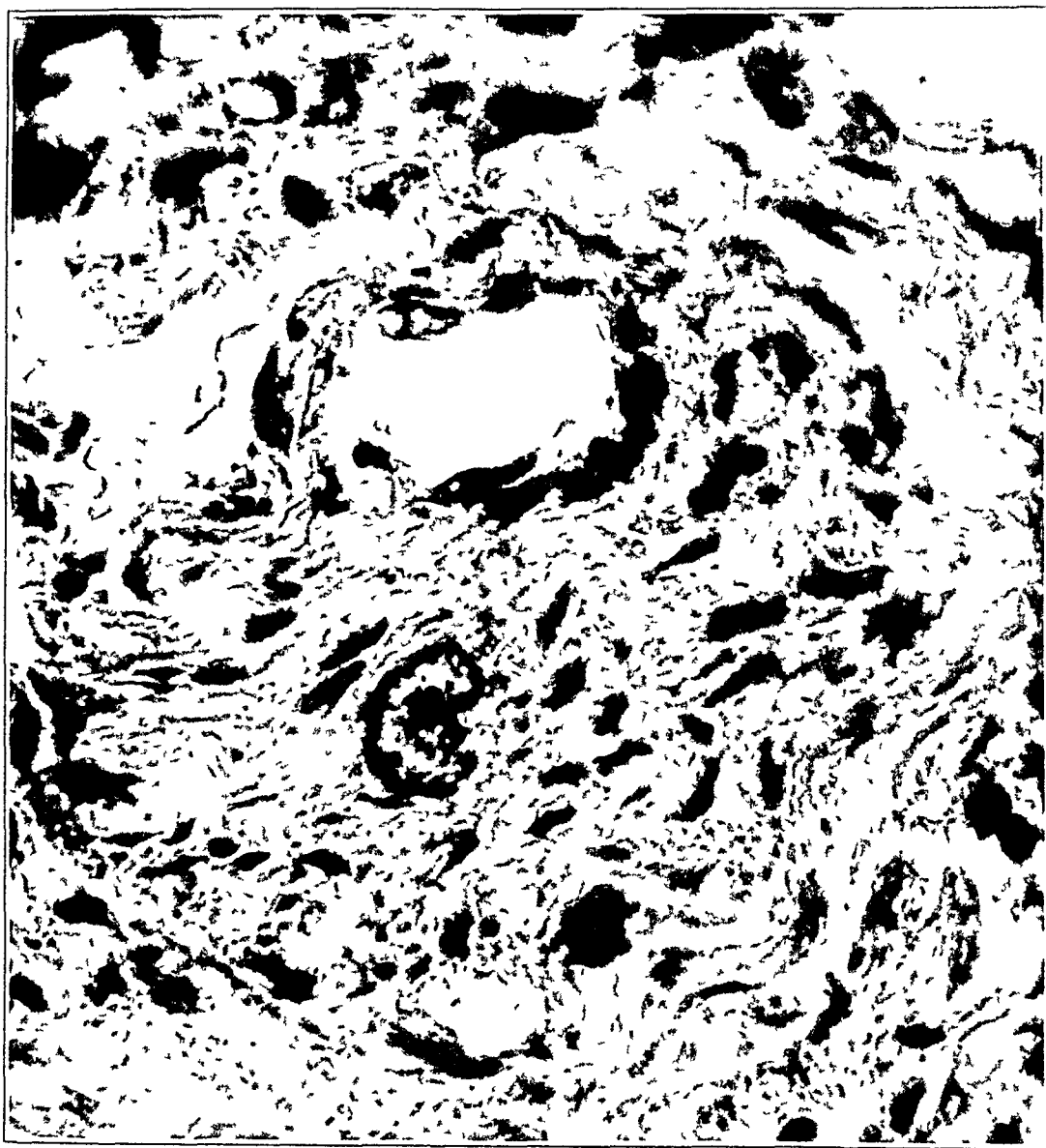


Fig 4—High power photomicrograph from a section of the lung, showing a blood vessel with a markedly narrowed eccentric lumen and a hyperchromatic carcinoma cell nucleus at the center of the thickened fibrous intima.

mucosa was firmly fixed to the underlying muscularis. This area was smooth and thin. The underlying serosa and the submucosa were thickened and fibrous, and fibrous strands were seen to extend through the muscularis. Several of the biliary lymph nodes were enlarged, they were firm and discrete and appeared cellular.

The thoracic organs were removed through the diaphragm. The right lung weighed 520 Gm, and the left, 460 Gm. Each exhibited moderate coal-dust mottling but no other gross changes. There was no gross evidence of metastatic carcinoma within the lungs. The tracheobronchial lymph nodes, however, were enlarged gray-black cellular structures and were obviously carcinomatous. The larger branches of the pulmonary artery were unchanged. The pericardial sac contained only a few cubic centimeters of free fluid and presented a smooth, gray inner surface. The heart weighed 340 Gm. The right ventricle was somewhat dilated, with the trabeculae carneae and papillary muscles somewhat enlarged. The myocardium of the right ventricle was 0.5 cm thick adjacent to the pulmonary ring and 0.8 cm thick distally. The valvular rings of the heart measured as follows: pulmonic, 8 cm, tricuspid, 13 cm, mitral, 9 cm, and aortic, 5.5 cm.



Fig 5—Photomicrograph of a section of the lung, showing a longitudinally cut blood vessel filled with fresh thrombus. The vessel is surrounded and somewhat compressed by lymphatic channels filled with metastatic carcinoma cells.

The coronary arteries were unchanged. The myocardium was firm and pale. The left chambers of the heart were unaltered. The conus arteriosus appeared to bulge somewhat anteriorly, without essentially altering the configuration of the heart.

Microscopic Postmortem Examination—Sections of the lungs showed many distinct carcinoma cells scattered throughout the perivascular and peribronchial lymphatic vessels. These carcinoma cells were polyhedral, with ovoid to spherical hyperchromatic nuclei. They showed no tendency to form glands, and little invasion of the pulmonary parenchyma was noted. The only evidence of actual invasion of the walls of the blood vessels was a single observation of a hyper-

chromatic carcinoma cell nucleus in the thickened fibrous intima of a small blood vessel (fig 4) Many of the blood vessels were obliterated by recent thrombi composed of strands of fibrin and evenly dispersed erythrocytes These thrombi were in blood vessels which were adjacent to, and which often appeared to be compressed by, lymphatic vessels abundantly filled with carcinoma cells (fig 5) In a few of the larger, yet microscopic, blood vessels mural thrombi were seen No carcinoma cells were identified in these thrombi, nor were any carcinoma cells seen invading the walls of the blood vessels in contact with these thrombi Many of the smaller arteries showed marked narrowing of the lumen, because of increased connective tissue of the intima Connective tissue in various stages of proliferation was seen, ranging from young fibroblasts to well developed



Fig 6—Photomicrograph of a small pulmonary blood vessel, showing an organized and canalized thrombus One channel occupying the left lower quadrant displays secondary occlusion, with more recent organization of the clot than is observed elsewhere Note the nests of carcinoma cells in the adjacent lymphatic ducts

collagen-containing strands This thickening of the intima resulted in varying degrees of narrowing of the vessels, and in some instances complete obliteration of the lumen had occurred Multiple channels of various sizes were seen to pass through this connective tissue, denoting recanalization of obstructed vessels A few of these newly formed channels were observed in turn to be occluded by secondary thrombosis and organization (fig 6) Some connective tissue was also observed in the adventitial region of the blood vessels

Sections of the stomach taken from the "smooth area" in the lesser curvature near the pylorus showed this area to be the seat of a carcinoma. Carcinoma cells were best seen on the mucosal surface. Here they were polyhedral and contained ovoid to spherical hyperchromatic nuclei. More deeply, spherical and polyhedral epithelial cells, occurring singly or in nests, were seen to invade the tunica propria. Mitotic figures were not numerous. There was some tendency to form small atypical glands, which were seen invading the submucosa and muscularis. This occurred especially in areas where there was an abundance of dense connective tissue containing collagen. The serosa was thickened by the presence of dense connective tissue, and in one section a dilated lymphatic vessel containing many carcinoma cells was noted. These cells were identical with those seen in the lymphatic vessels of the lung.

Sections of the heart showed slight enlargement of the muscle cells of the wall of the right ventricle. No changes were seen in the myocardial cells of the left ventricle.

COMMENT

This case is unique in that death was not due to massive carcinomatous metastases or to toxemia from the growth but resulted from circulatory failure due to obstruction of the pulmonary circulation beyond the point compatible with life. This obstruction was caused by extensive carcinomatous metastasis into the perivascular lymphatic vessels, which in turn produced arteriolar thrombosis, with organization and connective tissue proliferation. The changes in the arterioles appeared to be the results of three factors: (1) the mechanical factor of pressure from the adjacent cancer-filled lymphatic vessels, (2) an active invasion of the walls of the blood vessels by cancer cells and (3) the biologic factor of connective tissue proliferation stimulated by the presence of the desmoplastic tumor in the neighboring lymphatic vessels.

A fairly comprehensive search of the literature yielded only two comparable instances. One was reported by Schmidt¹⁷ 1903 as follows:

A man aged 37 years complained of slight gastric distress for several weeks, otherwise there were complete well-being and an excellent nutritional state. Death occurred suddenly. Autopsy revealed dilatation and some hypertrophy of the right ventricle, especially of the pulmonary cone. The lungs showed grossly numerous fine, white, ramified cordlike threads passing through all lobes of both lungs, corresponding to the distribution of the vessels. Nothing like this was noted in the pleurae. There were no tumors, nodules in the pulmonary tissue or cancerous deposits under the mucosa of the bronchi. Microscopically the small arteries in the lungs with a diameter of 0.75 mm or less were filled with thrombi of different structure. This has occurred so evenly and so extensively that in many sections hardly a single vessel of this caliber was unchanged. The lumen contained partly fibrinous, partly hyaline, granular thrombi and epithelial cells, which formed accumulations of a mosaic-like order and which when compared with the cells of the stomach and those of the lymph nodes were undoubtedly

17 Schmidt, M. B. Die Verbreitungswege der Karzinome und die Beziehung generalisierter Sarkome zu den leukamischen Neubildungen, Jena, Gustav Fischer 1903.

cancer cells. Nowhere in the carefully examined lungs could cancer cells be seen except in the lumen of the blood vessels. None were seen in the perivascular lymphatic vessels, the pulmonary tissue or the walls of the blood vessels.

In the stomach was noted a circular, infiltrating, almost completely ulcerated scirrhous carcinoma 1 to 2 cm above the end of the pyloric ring.

The postmortem diagnosis was carcinoma of the stomach, and the cause of death was regarded by the author as being related to the hypertrophy of the right side of the heart, which resulted from obstruction of the arterial circuit within the lungs by old organized thrombi. The sudden death was possibly due to the new import of cancerous material. Clinically, however, the presence of a cancerous lesion was not suspected, and no explanation could be given (*ante mortem*) for the enlargement of the right side of the heart.

The other patient was reported on by Kiutzsch¹⁰ (1920) as follows:

A 40 year old city clerk was admitted on Aug 27, 1917, to the city hospital of Dresden-Friedrichstadt. At the age of 17 the patient had a purulent infection of the right leg and the upper portion of the left arm. After an operation the condition was recognized as being of syphilitic origin and was cured with mercurialunctions and potassium iodide. One year previously symptoms suggestive of peptic ulcer appeared. For two months increasing tiredness, weakness and palpitation had been noted, and during the last three weeks the patient appeared pale.

Examination—The patient was of medium size and in a reduced state of nutrition and strength. The lips and nails were strongly cyanotic. Examination of the lungs revealed normal sounds, there were few bronchitic sounds. The heart was slightly broader toward the right, with impure tones. The pulse was small and rapid. The abdomen was soft, and the gastric region showed tenderness but no definite resistance. The liver was somewhat firm but not enlarged. The nervous system was normal. Examination of the urine revealed a trace of albumin but no sediment. The Wassermann reaction was negative.

Treatment—Caffeine, morphine and codeine were administered.

Course—There was an increasing decline, with frequent vomiting. The hemoglobin value was 65 per cent. A blood smear showed poikilocytosis and a normal proportion of leukocytes. Death occurred on August 31, four days after the patient's admission to the hospital.

The author stated that as for Schmidt's patient, the clinical history offered no explanation of the increase of the size of the right side of the heart. The clinical diagnosis was severe anemia, chronic gastric ulcer and endocarditis.

Postmortem Examination—The heart was slightly larger than the fist. The right chamber was 10 cm long and somewhat dilated, the musculature was 8 mm thick and imparted a feeling of stiffness, the papillary muscles and trabeculae were prominent. The left chamber was 9 cm long, and its wall was 12 mm thick.

The lungs were large and contained air. The pulmonary tissue was a little denser than normal. The surface showed extraordinarily numerous fine grayish white linear markings in reticular order, which corresponded to the generally bluish lymphatic vessels in the visceral pleura. The pleura was smooth and shiny. The fine white linear markings stood out somewhat from the surface. Sectioned tissue was grayish red. Extraordinarily numerous white lines, about 0.25 to 0.5 mm wide, were prominent and corresponded to the borders of the lobules. Grossly no changes were evident in the blood vessels of the lung. Microscopically, practically all the smaller arteries of the lung (at least three fourths of them) had become

plugged by thrombi. Some were old, and the plugs were intimately united with the walls. Sections through these thrombi no longer revealed definite evidence of carcinoma cells. In other sections the fibrosis had not progressed so far, and there were still some small but definitely recognizable accumulations of cancer cells visible amid the connective tissue coming from the wall. Occasionally in an old thrombus there were seen newly formed vessels running parallel to the axis of the old vessels. Often in the newly formed vessels were seen carcinomatous emboli, which appeared freshest and most viable because the nuclei were strongly stained. At least as numerous as in the blood vessels were the carcinomatous plugs in the lymphatic vessels of the lungs, where the entire picture gave the impression of a young, strongly proliferative formation. Obliteration with carcinomatous plugs was noted in the peribronchial, perivascular, interalveolar and subpleural lymphatic vessels. In longitudinal sections the completeness of the filling of the lumen was evident. The caliber of the lymph vessels was enlarged. Whenever a network of cancer-filled perivascular lymphatic vessels surrounded a thin-walled artery, the latter was obliterated through pressure exerted on it by these lymphatic vessels. No cancer cells were seen anywhere outside the vascular structures. The pulmonary parenchyma showed evidence of only passive congestion.

The stomach showed a carcinomatous ulcer of the small curvature. The lesion was about 8 cm. in length, and at places 2.5 cm. in thickness.

In conclusion the author remarked that by the obstruction (thrombosis) of the pulmonary circulation the lesser circuit was gravely disturbed. The fully organized thrombi and the long duration of the process were evidently responsible for the hypertrophy of the right side of the heart.

The three patients whose histories have been described showed strikingly similar conditions both clinically and pathologically. Their ages were 36, 37 and 40 years, respectively. They each suffered from gastric distress for about a year. In two instances a diagnosis of peptic ulcer was made. In all three patients, without any previous history of cardiopulmonary disease, there developed rapidly (in a few days or weeks) symptoms of strain of the right side of the heart. For two of the patients either a diagnosis of endocarditis was made or the presence of this condition was suspected. For none was there an adequate explanation (*ante mortem*) of the strain of the right side of the heart. Pathologically the end-results were identical for all three patients, namely, hypertrophy and dilatation of the right side of the heart due to extensive obstruction of the pulmonary circulation. In Schmidt's patient the obstruction was limited to the arterioles, in Krutzsch's patient the lymphatic vessels and the arterioles were equally affected, in our patient the primary involvement was apparently in the perivascular lymphatic vessels, and the arteriolar obstruction was secondary.

In all three patients the immediate cause of death was failure of the right side of the heart which had developed more or less suddenly after a relatively brief period (of from two weeks to two months) of illness characterized by symptoms of strain of the right side of the heart. It is suggested that this clinical picture is most accurately

described by the term subacute cor pulmonale. It is further suggested that this subacute type of cor pulmonale may be differentiated clinically from either the acute or the chronic type. In the former the onset is explosive, with a great deal of shock, often associated with pain, and is not preceded by any period of insidious symptoms of strain of the right side of the heart. The patient with the chronic type of cor pulmonale generally presents clear evidence of the causative factors for many years, and relatively rarely when clear evidence of the causative factor is absent, the symptoms of strain of the right side of the heart continue for many years or at least for many months before death ensues from failure of the right side of the heart. In the reports of the cases of primary pulmonary arteriosclerosis collected by Brenner⁹ the duration of symptoms of strain of the right side of the heart was stated as having been from five months to five years, the average being about two years.

So far as we know no pathologic process other than that presented by the three patients included in this report has ever been noted in association with a clinical picture like the one here described under the term subacute cor pulmonale. If this observation is correct, it is probable that subacute cor pulmonale, as described in this communication, is a distinct clinicopathologic entity which can be recognized clinically. Its chief distinguishing feature is the rapid development of signs and symptoms of strain of the right side of the heart in a patient who gives no history of antecedent cardiopulmonary disease or any other condition known to be capable of producing strain of the right side of the heart. A history of "peptic ulcer" or of vague gastric discomfort over a period of several months or a year offers additional suggestive evidence. However, although in all three patients the primary lesion was in the stomach, the possibility must be admitted that a similar clinicopathologic picture may arise from a carcinoma originating in some other organ. Schmidt¹⁷ observed cancerous metastasis in the pulmonary vessels in fifteen of forty-one patients with carcinoma. In seven of these fifteen patients the primary growth was in the stomach, in the remaining eight the primary growth was in other organs of the abdomen and pelvis. But in only one of the fifteen (the patient whose case is reviewed in the present report) was the involvement of the pulmonary vascular tree sufficiently extensive to produce subacute cor pulmonale.

The type of cardiac failure which occurred in these three patients appears to be comparable to the cardiac failure resulting from graded compression of the pulmonary artery of dogs described recently by Fineberg and Wiggers.¹⁸ These investigators have shown that the right

18 Fineberg, M. H., and Wiggers, C. J. Compensation and Failure of the Right Ventricle, *Am Heart J* **11** 255-263 (March) 1936.

ventricle is able to compensate compression of the pulmonary artery up to an average of about 58 per cent, and up to that point there is no measurable change in the output of the left ventricle. Under these circumstances the aortic pressure is unchanged, and the systemic circulation remains adequate. During this time the right ventricle gradually hypertrophies and becomes accommodated to the increased load. If the resistance in the pulmonary circulation is increased beyond the point of potential compensation (i. e., more than the 58 per cent of average compression), the right ventricle distends, and the venous pressure rises. A lessened amount of blood is propelled through the pulmonary bed into the systemic circulation, and there is a drop in the aortic pressure. Owing to the fact that a lessened amount of blood becomes available for the coronary circulation, a vicious circle is established which accelerates the failure of the right ventricle. At this stage death may result from congestive failure or from a failure of the pacemakers, in which case the heart stops completely, and death takes place before there is time for marked congestive failure to occur.

It seems probable that the last-mentioned mechanism supervened in the three patients reported on here. There was but slight passive congestion evident at necropsy in all three instances. In two of the patients death was apparently sudden. In our own patient it was noted that during the last hour of life the pulse could not be felt. Finally the heart stopped, while breathing still continued. It is regrettable that electrocardiograms are not available. Much interesting information might have been derived from serial tracings picturing the events in the final hours of life.

The entire record suggests that here nature has duplicated the experiment of "graded compression of the pulmonary artery." The sections from the lungs indicated that at the time of death there was more than 60 per cent obliteration of the pulmonary vascular bed, and yet no symptoms of strain of the right side of the heart appeared until about ten days before death, and alarming symptoms did not become manifest until the last forty-eight hours of life. At necropsy the right ventricle showed relatively mild hypertrophy, although roentgenographic examination two days before death disclosed marked dynamic dilatation of the pulmonary conus.¹⁹ Thompson and White³ estimated that strain for about two months is necessary to produce appreciable hypertrophy of the right ventricle. The degree of hypertrophy of the right ventricle in our patient and the time of the appearance of symptoms might suggest that the pulmonary vascular invasion by the carcinoma had been in progress for three or four months and that the appearance of

19 Dynamic dilatation of the pulmonary artery and conus that is seen during life may be absent at necropsy. Similar cases have been reported on by J. B. Schwedel and B. S. Epstein (*Am Heart J* 11: 292-302 [March] 1936).

symptoms ten days before death marked the point at which the obliteration of the pulmonary vascular bed reached a degree in excess of the limit to which the right ventricle was able to become adjusted. From this point on the downward progress was rapid, just as was noted in the experiments on animals conducted by Fineberg and Wiggers¹⁸

SUMMARY

The record of a patient whose death from failure of the right side of the heart resulted from rapid obstruction of the pulmonary circulation is presented. Both the pulmonary lymphatic vessels and the pulmonary arterioles were involved. The obstruction in the lymphatic vessels was the result of extensive invasion by metastatic carcinoma. The changes in the arterioles consisted of thrombosis with organization, intimal connective tissue proliferation and occasional invasion of the walls of the vessels by carcinoma cells. These changes were interpreted as the result of three factors: (1) pressure effects from the adjacent cancer-laden lymphatic vessels, (2) connective tissue proliferation due to the desmoplastic nature of the growth and (3) direct contact invasion of the walls of the blood vessels. The original tumor arose from the stomach, and its presence remained clinically unsuspected.

Reports of two comparable cases found in the literature are reviewed. These three records are strikingly similar, and it is suggested that they represent a clinicopathologic entity which may best be described by the term *subacute cor pulmonale*.

Dr William Shea permitted us to examine the clinical records and make a postmortem examination in this case.

RELATION OF KIDNEYS TO BLOOD PRESSURE

EFFECTS OF EXTRACTS OF KIDNEYS OF NORMAL DOGS
AND OF DOGS WITH RENAL HYPERTENSION
ON BLOOD PRESSURE OF RATS

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Goldblatt and his co-workers¹ have recently shown that a sustained increase in blood pressure may be produced in dogs by partial occlusion of the renal arteries. This observation has been confirmed by numerous investigators, including Page,² Prinzmetal and Friedman³ and ourselves. Since the hypertension is not relieved by denervation of the kidney, can be produced in animals subjected to previous renal denervation² and occurs even when the kidney has been transplanted into the neck,⁴ the rise in blood pressure appears to be of "chemical" rather than "nervous" origin.

Hartwich⁵ showed that ureteral ligation caused a rise in blood pressure in dogs. Similar results were reported by others,⁶ who found that

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1 Goldblatt, H., Lynch, J., Hanzal, R. F., and Summerville, W. W. Studies on Experimental Hypertension. Production of Persistent Elevation of Systolic Blood Pressure by Means of Renal Ischemia, *J. Exper. Med.* **59** 347, 1934

2 Page, I. H. The Relationship of the Intrinsic Renal Nerves to the Origin of Experimental Hypertension, *Am. J. Physiol.* **112** 166, 1935

3 Prinzmetal, M., and Friedman, B. Pressor Effects of Kidney Extracts from Patients and Dogs with Hypertension, *Proc. Soc. Exper. Biol. & Med.* **35** 122, 1936

4 Blalock, A., and Levy, S. E. Unpublished observations

5 Hartwich, A. Der Blutdruck bei experimenteller Uramie und partieller Nierenausscheidung, *Ztschr. f. d. ges. exper. Med.* **69** 462, 1930

6 Harrison, T. R., Mason, M. F., Resnik, H., and Ramey, J. Changes in Blood Pressure in Relation to Experimental Renal Insufficiency, *Tr. A. Am. Physicians* **51** 280, 1936

previous denervation of the kidney did not prevent the effect. It has recently been observed⁷ that ureteral ligation may cause a well marked diminution of the blood flow through the kidneys of unanesthetized dogs. Since ischemia of the kidneys should occur both after ureteral ligation and after the partial obstruction of the renal arteries, it seems that this functional change possibly is related in some way to the rise in blood pressure which occurs subsequent to these procedures.

The observations which have been cited on the denervated and transplanted kidney suggest that the rise in blood pressure may be brought about by some substance formed in the ischemic kidneys which reaches the rest of the body through the blood stream. However, attempts made by Page⁸ and Prinzmetal and Friedman³ to demonstrate such a pressor substance in the blood of animals with hypertension due to renal ischemia yielded negative results. In experiments previously reported⁹ the problem was approached from a different angle, the pressor effects of extracts of normal and of ischemic kidneys being compared in unanesthetized dogs. It was found as a general rule that the extracts of ischemic kidneys caused a greater rise in blood pressure. Similar results were reported by Prinzmetal and Friedman³. However, interpretation of these findings was complicated by the fact that in dogs the renal extracts usually produced an initial decline in blood pressure, collapse occurring frequently and death occasionally. Furthermore, it was found⁹ that depressor effects were more frequently encountered after the injection of extracts of normal kidneys than after the injection of extracts of ischemic kidneys. It was therefore uncertain whether the greater rise in blood pressure following the administration of extracts of ischemic kidneys was due to an increased amount of pressor material or to a decreased amount of depressor substance in these as compared with normal kidneys.

Attempts were next made to separate pressor and depressor agents by subjecting the renal extracts to various methods of purification. The attempts were only partially successful. Certain facts were learned concerning the chemical nature of the renal pressor substance,¹⁰ which

7 Levy, S. E., Mason, M. F., Harrison, T. R., and Blalock, A. The Effects of Ureteral Occlusion on the Blood Flow and Oxygen Consumption of the Kidneys of Unanesthetized Dogs, *Surgery* **1** 238, 1937.

8 Page, I. H. Vaso-Pressor Action of Extracts of Plasma of Normal Dogs and Dogs with Experimentally Produced Hypertension, *Proc Soc Exper Biol & Med* **35** 112, 1936.

9 Harrison, T. R., Blalock, A., and Mason, M. F. Effects on Blood Pressure of Injection of Kidney Extracts of Dogs with Renal Hypertension, *Proc Soc Exper Biol & Med* **35** 38, 1936.

10 Mason, M. F., Williams, J. R., Jr., and Harrison, T. R. Observations on Two Different Pressor Substances Obtained from Extracts of Renal Tissue, to be published.

could be freed, in large measure, of depressor agents, but it has not been possible as yet to recover it quantitatively. Therefore, no attempt has been made to compare the pressor properties of purified extracts from normal kidneys and those from ischemic kidneys.

We have recently found that rats anesthetized with pentobarbital sodium display little or no depressor reactions to the injection of renal extract. The use of these animals as test objects has allowed us to compare again the pressor activity of extracts from normal and extracts from ischemic kidneys under conditions which are not complicated by the confusing effects of collapse and other untoward reactions.

In 1898 the pressor property of renal tissue was reported by Tigerstedt and Bergman,¹¹ who found that saline extracts of the kidneys of rabbits produced a well marked increase in blood pressure when administered intravenously to other rabbits. They named the active principle renin. Shaw¹² confirmed these observations, using cats as test animals. He also found, as had Vincent and Sheen,¹³ that the renal extracts often had a marked preliminary depressor action. Shaw emphasized that the results obtained were influenced by the type and depth of anesthesia. Bingel and Strauss¹⁴ used the autolyzed press juice of kidneys and made similar preparations from most of the other tissues of the body. The juice from the latter usually caused a decline in blood pressure, while that from the kidneys had a pronounced pressor effect. More recently the pressor action of preparations of renal tissue has been confirmed by Thauer¹⁵ and by Hartwich and Hessel¹⁶. The latter authors made extensive investigations of the properties of renin. Hessel and Maier-Huser¹⁷ reported that they had been able to purify renin and had obtained it in a powdered form free from histamine and other depressor substances, but they did not give their method of purification. The

11 Tigerstedt, R, and Bergman, P. G. Niere und Kreislauf, Skandinav. Arch. f. Physiol. **8** 223, 1898.

12 Shaw, H. B. Autointoxication. Its Relation to Certain Disturbances of Blood Pressure, *Lancet* **1** 1295 and 1375, 1906.

13 Vincent, S., and Sheen, W. The Effects of Intravascular Injections of Extracts of Animal Tissues, *J. Physiol.* **29** 242, 1903.

14 Bingel, A., and Strauss, E. Ueber die blutdrucksteigernde Substanz der Niere, *Deutsches Arch. f. klin. Med.* **96** 476, 1909.

15 Thauer, R. Die Wirkung von Nierenpress-saften und-Extrakten auf den Blutdruck von Versuchstieren, *Zentralbl. f. inn. Med.* **54** 2, 1933.

16 Hartwich, A., and Hessel, G. Experimentelle Untersuchungen zur Kreislaufwirkung korpereigener Stoffe, *Zentralbl. f. inn. Med.* (no 18a) **53** 612, 1932. Hessel, G., and Hartwich, A. Chemische Eigenschaften des blutdrucksteigernden Prinzips in Nierenautolysaten, *ibid.* **53** 626, 1932.

17 Hessel, G., and Maier-Huser, H. Ueber das Renin, einen korpereigenen kreislaufwirksamen Stoff, *Verhandl. d. deutsch. Gesellsch. f. inn. Med.* **46** 347, 1934.

observations of others¹⁰ were in agreement with those of previous workers in indicating that renin is a protein and suggested that it has certain properties resembling those of the pseudoglobulins

Several authors investigated the site of action of renin and found that it acted directly on the blood vessels, the pressor effect being observed after decapitation, chondotomy and vagal section. There was a pronounced constrictor action in isolated preparations.

The object of our experiments has been to determine whether or not the pressor substance described by various authors as being present in renal tissue could be demonstrated in greater quantities in the kidneys of animals with experimental renal hypertension.

METHOD

Hypertension was produced in one group of dogs by the application of a Goldblatt clamp to one renal artery, the kidney being explanted to the flank and the opposite kidney being subsequently removed. After a significant rise in blood pressure had occurred, the ischemic kidney was removed under local anesthesia. For purposes of comparison, normal kidneys were taken from healthy dogs killed by bleeding from an arterial cannula inserted while the area was under local anesthesia. Extracts were made also from the normal and abnormal kidneys of dogs in which hypertension had developed as the result of the application of a clamp to one renal artery. The blood pressure of the dogs was measured either by puncture of the femoral artery with a needle or by means of the cuff described by Ferris and Hynes,¹⁸ the passage of the pulse wave being determined by palpation of the dorsal artery of the foot.

The freshly removed kidneys were weighed, chopped into fine particles with scissors, ground in a mortar with carborundum and physiologic solution of sodium chloride, which was added in a ratio of 2 cc for 1 Gm of kidney. After thorough grinding, the suspension was centrifugated. The supernatant fluid was kept in the icebox and again centrifugated before injection. Large rats, weighing from 300 to 500 Gm, were anesthetized by the intraperitoneal injection of pentobarbital sodium, the dose being approximately 4 mg per hundred grams. A needle (16 or 18 gage) was tied into the lower portion of the abdominal aorta, and the mean blood pressure was measured on a mercury manometer. The manometer tubing had such a small bore that a satisfactory float could not be devised. Consequently, no graphic record was made, the blood pressure being read and recorded every fifteen seconds. The manometer was attached to the needle by means of a three way tap, through which injections could be made into the aorta. In order to standardize the procedure, all injections were made at a rate of 1 cc in fifteen seconds. The amount of renal extract injected varied from 0.25 to 1.5 cc, the usual amount being 1 cc.

Preliminary observations with this technic showed that mechanical effects on the blood pressure due to the increase in the volume of blood usually reached a maximum within a few seconds after the end of the injection, while pressor

18 Ferris, H. W., and Hynes, J. F. Indirect Blood Pressure Readings in Dogs. Description of Method and Report of Results, *J. Lab. & Clin. Med.* **16**: 597, 1931.

responses to renal extract did not reach a peak for one or more minutes. Consequently, readings obtained during the first thirty seconds after the injection have been discarded. Since slow spontaneous rises in blood pressure sometimes occurred, increases appearing more than five minutes after the injection also have been neglected.

The rises in blood pressure have been computed by comparing the average of the three highest successive readings noted after the administration of renal extract with the average value during the minute prior to the injection.

It was soon found, as previously noted by Bingel and Strauss,¹⁴ that successive injections of the same dose of the same renal extract caused progressively less pressor effect (chart 1), the blood pressure tending to become stabilized at a somewhat higher level after each injection. Consequently, for comparative purposes the response to a given injection has been compared not with the effect

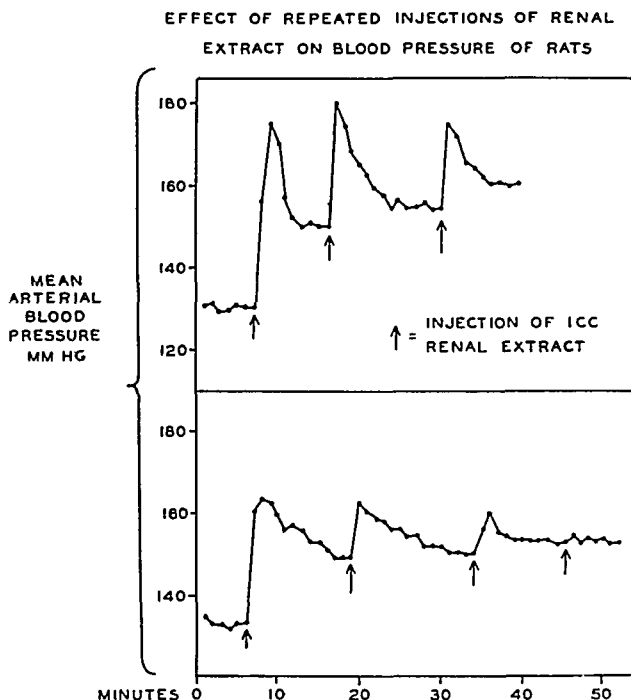


Chart 1—In each experiment the same extract was injected repeatedly. In both the first injection produced a greater rise in blood pressure than did the second, which caused a more marked response than did the third. After each injection there was a tendency for the blood pressure to become stabilized at a somewhat higher level.

of the preceding or succeeding injection but with the average of the effects of the two injections, the extract of normal and that of ischemic renal tissue being administered alternately.

RESULTS

Forty-seven comparisons were made (nineteen different rats being used) between the pressor effects of ischemic kidneys from six dogs with hypertension and the normal kidneys of five dogs with normal

blood pressure The data are presented in table 1 and illustrated in chart 2 In two instances the "normal extract" caused a greater rise in blood pressure than did the "ischemic extract" The latter was more pressor in thirty-four instances Eleven comparisons were regarded as inconclusive, i e, the differences were less than 5 mm of mercury

Thirty-three comparisons were made (fourteen different rats being used) between the pressor effects of the normal and those of the ischemic kidney of the same dog Twice the "normal extract" gave greater

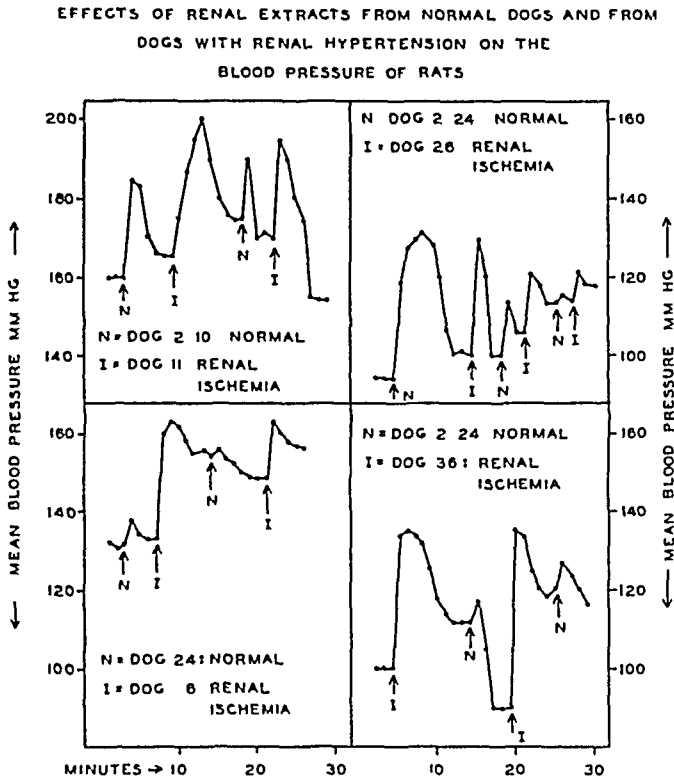


Chart 2—Four comparisons are shown of the pressor effects of extracts of kidneys of normal dogs and of extracts of kidneys of dogs with hypertension due to renal ischemia In three of the experiments it is obvious that the latter extracts had a more pronounced pressor effect The results of the fourth comparison (upper right graph) are less definite This rat became markedly less sensitive as the injections were repeated When the response to the "ischemic extract" is compared with that of the preceding injection of "normal extract," there is apparently little difference However, when the effect of the second injection is compared with the average effect of the first and the third, when the effect of the third is compared with the average effect of the second and the fourth and so forth, it is seen that the "ischemic extract" is definitely more effective than the "normal extract"

effects, twenty-two times the "ischemic extract" was more effective, nine comparisons were inconclusive The data are presented in table 2 and graphically in chart 3

TABLE 1—*Effects of Injection of Saline Extracts of Normal and Ischemic Kidneys of Different Dogs on the Arterial Blood Pressure of Rats**

Rat No	Rise in Blood Pressure, Mm Hg †		Dogs from Which Kidneys Were Obtained				
			Normal kidney		Ischemic kidney		
	From Normal Kidney	From Ischemic Kidney	Dog No	Blood Pressure, Mm Hg	Dog No	Blood Pressure Before Opera- tion	Blood Pressure When Kidney Was Removed
2 11 5	5 9 12	36 30 25	2 10	Not taken	11	122	180
2 12 5	35 30	42 38					
2 12 3	20 15	35 30					
2 13 1	6 0 0 0	18 11 13 15					
2 16 4	0	28	24	128	6	126	166
2 16 3	11	32					
2 16 2	6 3 0	14 4 6					
2 16 1	3 0 0 0	30 21 10 5					
2 22 8	1 0	19 12	24	128	20	119	162
2 22 6	4	11					
2 22 5	11 12	21 16	92‡	154			
2 22 7	8 5	11 6	24	128	22	124	165
2 22 8	2 5	5 5					
2 22 5	11	10	92‡	154			
2 22 2	18 0	4 3	74C (Mange, severe anemia)	134			
2 22 1	25	16					
2 24 1	8 3	24 18	24	128	36	130	186
2 24 2	4 6	40 45					
2 24 3	0	25					
2 24 3	8	10	224	118			
2 24 4	13 7 0	13 13 10	74C	134	26	135	173
2 24 4	8	16	224	118			
2 24 5	26 14 9 3	30 22 14 10					

* Summary Ischemic kidney greater than normal kidney (by 5 mm or more) 34 times
 Normal kidney greater than ischemic kidney (by 5 mm or more) 2 times
 Inconclusive (i e, difference of less than 5 mm) 11 times

Total number of comparisons

47

† The black figures represent the average effect of two injections one before and one after the response shown in the opposite column

‡ This dog has a clamp on the renal artery of the other kidney

In view of the inherent difficulties in such a method of biologic assay due to differences in the sensitivity of different animals and to spontaneous variations in blood pressure and with allowances made for the pronounced although irregular decreases in responsiveness to repeated injections of the same extract, it seems that the few exceptional results can be neglected as being due to experimental error. We therefore believe that the observations indicate that—so far as can be judged from the test object employed—extracts of ischemic kidneys obtained from dogs with experimental renal hypertension have a more pronounced pressor effect than do extracts of normal kidneys of dogs. The difference is apparently due not to differences in content of depressor substance but to an excess of pressor substances. It should be emphasized, however, that the difference between normal and ischemic kidneys is

EFFECTS OF EXTRACTS OF NORMAL (N) AND ISCHEMIC (I) KIDNEYS
FROM THE SAME DOG ON THE BLOOD PRESSURE OF RATS

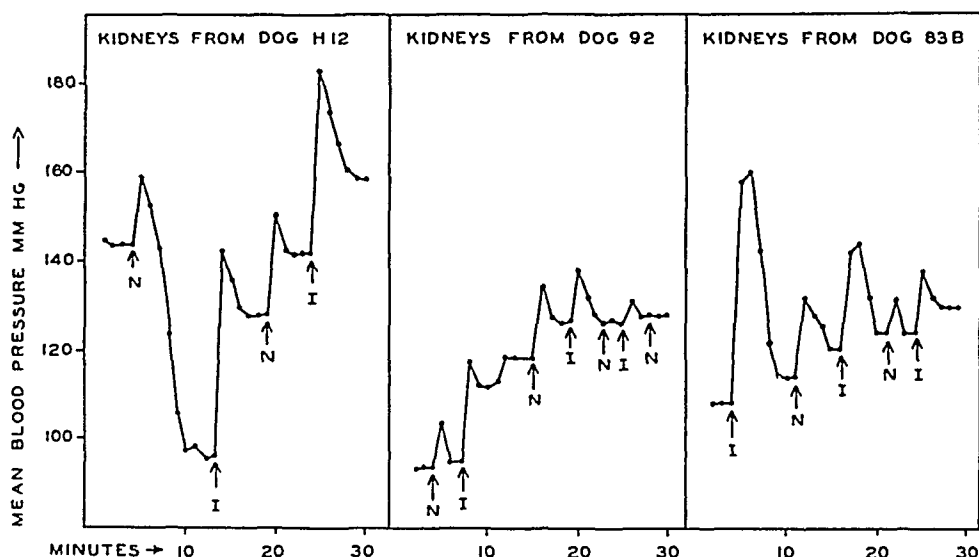


Chart 3—The kidneys were removed from three dogs each of which had hypertension as the result of partial obstruction of one renal artery. The pressor property of the ischemic kidney was compared with that of the normal kidney of the same dog. In each instance the extract of the ischemic kidney caused a greater rise in blood pressure than did that of the normal kidney.

quantitative rather than qualitative, for all the normal kidneys tested had definite pressor effects when sufficient amounts were injected into sensitive animals.

In order to determine whether ischemia of organs other than the kidney leads to the appearance of increased amounts of pressor substances, the following observations were made. Partial occlusion of one of the main branches of the splenic artery and of the left renal artery of a dog was induced with Goldblatt clamps. A main branch of the

hepatic artery was ligated Five days later the animal was killed, and saline extracts were made of normal and of ischemic tissue of the spleen, liver and kidney All these extracts had pressor effects when injected into rats However, the responses to the extracts of liver and spleen

TABLE 2—*Effects of Injection of Saline Extracts of Normal and Ischemic Kidney of Same Dog on the Arterial Blood Pressure of Rats **

Rat No	Rise in Blood Pressure, Mm Hg †		Dog from Which Kidneys Were Obtained		
	From Normal kidney	From Ischemic Kidney	Dog No	Blood Pressure, Mm Hg	
				Average Before Operation	When Kidneys Were Removed
2 19 6	13	16	H12	129	172
2 19 5	18	46			
	21	42			
2 19 4	2	4	92	98	158
	4	10			
2 19 3	5	12			
2 20 1	0	12			
2 22 6	14	22			
2 22 4	15	22			
	16	17			
	8	12			
	1	8			
	1	5			
2 22 3	3	7			
	1	6			
2 25 4	18	38	S3B	137	164
	13	24			
	8	19			
2 25 3	10	20			
	14	17			
	14	14			
2 25-2	0	23			
2 25 1	12	20			
	15	17			
	28	19			
	30	22			
2 26 1	23	51			
	20	37			
	14	23			
	7	17			
2 26 2	0	23			
	1	15			
	1	14			

* Summary Ischemic kidney greater than normal kidney (by 5 mm or more) 22 times
 Normal kidney greater than ischemic kidney (by 5 mm or more) 2 times
 Inconclusive (i e, difference of less than 5 mm) 9 times

Total number of comparisons

33

† The black figures represent the average effect of two injections, one before and one after the response shown in the opposite column

were different—being of shorter duration—from the more sustained effects produced by the extracts of the kidneys Furthermore, the ischemic renal tissue had a more pronounced pressor effect than did the normal renal tissue, but no such differences were observed in the case of the preparations from the other organs (chart 4 A) Since it has been shown¹⁰ that pressor effects due to a tyramine-like substance may be obtained from organs other than the kidney, extracts were also pre-

paired by grinding the tissues in alcohol and testing the water-soluble fractions of the alcohol-insoluble portions (Since tyramine is soluble in alcohol and the specific renal pressor substance is not, this procedure allows one to separate the two principles) The results (chart 4 *B* and *C*) showed clearly that ischemic liver and ischemic spleen do not contain detectable amounts of the specific renal pressor substance In the case of the kidney, however, the alcohol precipitates from the ischemic organ were more actively pressor than the same fractions from the normal organ It therefore appears that the increased pressor effect obtained from ischemic renal tissue is due to an increase in the concentration of the renal pressor substance (Tigerstedt's renin)

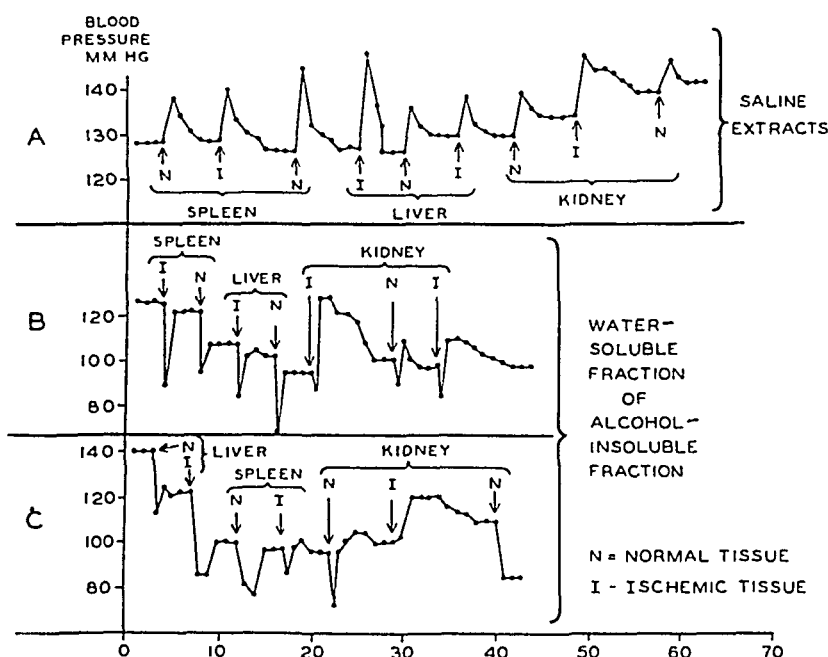


Chart 4—*A*, pressor effects were obtained from saline extracts of all the tissues. However, in the case of the liver and spleen the extracts of the ischemic tissues showed no greater action than did the preparations from the normal tissue. The duration of the pressor effects was longer with renal extracts, and the usual difference between normal and ischemic kidneys was found *B* and *C*, when extracts prepared by precipitation with alcohol were tested, only depressor responses were obtained from the liver and spleen. However, the same method of preparation yielded pressor renal extracts, the ischemic kidney being more active than the normal kidney.

COMMENT

The findings which have been reported naturally suggest that the increase in blood pressure produced in animals by experimental renal ischemia is dependent on the excessive formation of a pressor agent which is also present in normal kidneys. However, several other possibilities suggest themselves. The substance formed in the kidney with a defective blood supply might be somewhat different in chemical con-

stitution and therefore more active pharmacologically. It is also possible that the kidney with an impaired circulation is less capable of excreting the pressor substance than is the normal kidney, which forms it in equal amounts. Again, one can conceive of the pressor agent as a product of some intermediary metabolic process in the kidney, the reaction failing to go on to completion in the absence of an adequate blood supply. Furthermore, the possibility remains that the occurrence of an increased pressor activity in the ischemic kidney is purely incidental and bears no relation to the rise in blood pressure exhibited by the animal. Conclusions in regard to these questions as well as concerning the problem of the possible relation of the findings reported to renal hypertension in man cannot be drawn until further evidence is available.

SUMMARY

The administration of saline extracts of the kidneys of normal dogs to rats anesthetized with pentobarbital sodium usually causes a significant rise in blood pressure. Similar extracts of the kidneys of dogs rendered hypertensive by compression of the renal arteries cause a more marked increase in the blood pressure of the recipient animals. Comparisons of extracts prepared from the two kidneys of dogs rendered hypertensive by compression of one renal artery have shown a distinctly greater pressor effect from the abnormal than from the normal kidney. The possible relation of the findings to the mechanism of the hypertension produced by compression of the renal arteries has been discussed.

MULTIPLE MYELOMA

REPORT OF FOUR CASES, WITH HYPERPROTEINEMIA IN TWO

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Four patients with multiple myeloma of the plasma cell type were studied clinically and pathologically at the Montreal General Hospital during 1934 and 1935. The occurrence of unusual features, such as hyperproteinemia in two instances and absence of Bence-Jones protein in three instances, seemed to justify publication of a detailed report. The occurrence of these four cases within a period of eighteen months was of further interest, as no other established cases were recorded during the fifteen year period from 1921 to 1936.

REPORT OF CASES

CASE 1—P. J., an Ethiopian aged 42, was admitted to the service of Dr. C. P. Howard on Aug. 6, 1935, complaining of weakness and pain in the lower portion of the back of three weeks' duration.

Family History—His family history was not remarkable, in that his parents had died of unknown causes, and his brothers and sisters were alive and well.

Personal History—The patient was born and bred in British Guiana. He worked as a police officer in Guiana, a miner in Nova Scotia and a laborer in Cuba and Montreal. He contracted pneumonia in 1913 and influenza in 1917 and was admitted to the Montreal General Hospital in 1927 with a diagnosis of duodenal ulcer and latent syphilis. After discharge he was treated for three years in the outpatient department of the hospital and was reported cured.

History of Present Illness—The patient was in good health until three weeks before admission to the hospital, when he noticed slight stiffness and pain in the lower portion of the back on bending. The pain and weakness in the lumbar and sacro-iliac regions became more pronounced in spite of the application of a belladonna plaster. The day prior to his admission to the hospital he worked with pick and shovel until 2 p. m., when he had to be assisted home because of severe pain in his back.

Examination—The temperature was 97° F., the pulse rate 72 and the weight 145 pounds (65.8 Kg.). The patient was a well developed and fairly well nourished Ethiopian. He appeared to have severe pain in the lumbar region on the slightest movement. The head, nose, throat and mouth were not remarkable. The lungs were clear. The heart was slightly enlarged, both to the right and to the left, and there was a localized apical systolic murmur. The blood pressure was 112

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systolic and 80 diastolic The abdomen was normal There was a purulent urethral discharge of gonorrheal etiology Examination of the back revealed no tenderness over the spines of the vertebrae or the sacro-iliac joints There was, however, pain in the lumbosacral region on the slightest movement

Laboratory Data—Urine The urine was clear and had a specific gravity of 1.016 Neither albumin nor sugar was present There were from 4 to 9 pus cells per high power field

Blood A blood count showed 3,320,000 red blood cells, 6,400 white blood cells and 70 per cent hemoglobin (Hellige) A differential count showed polymorphonuclears, 67 per cent, lymphocytes, 27 per cent, eosinophils, 2 per cent and monocytes, 4 per cent The van den Bergh test showed 0.2 units

Chemical analysis of the blood showed urea nitrogen, 11 mg, creatinine, 1.96 mg, uric acid, 5.71 mg, and sugar, 140 mg, per hundred cubic centimeters The Wassermann reaction was negative The complement fixation test for gonococci gave a positive reaction

Spinal Fluid The Wassermann reaction of the spinal fluid was negative, but the Pandy reaction was positive

Diagnosis—In view of the character of the pain and the chronic gleet, a diagnosis of gonorrheal arthritis was entertained However, when roentgenograms of the area involved were taken, they showed multiple circumscribed rarefied areas suggestive of multiple myeloma The subsequent investigation served to confirm this diagnosis

Further Laboratory Data—Roentgenograms Further roentgenograms showed rarefied areas throughout the skull, vertebrae, pelvic bones, femurs and ribs The pulmonary fields were clear The tibiae were not involved

Metabolism The basal metabolic rate was -11 per cent

Blood Further study of the blood was made

	Nov 12	Aug 21	Aug 26	Sept 6
Total proteins, Gm per 100 cc	12.39	12.58	12.88	13.06
Albumin, Gm per 100 cc	2.45	2.36	2.87	
Globulin, Gm per 100 cc	9.59	9.96	9.77	
Fibrinogen, Gm per 100 cc	0.35	0.26	0.24	

The calcium content was 13 mg and the phosphorus content 3.52 mg per hundred cubic centimeters

The Bence-Jones proteose was never demonstrated either in the urine or in the blood plasma, although an unidentified proteose was precipitated from both plasma and urine at 56 C

A hemogram on August 28 showed red blood cells, 2,720,000, white blood cells, 11,500, hemoglobin, 48 per cent, platelets, 126,000, reticulocytes, 0.5 per cent, and diameter of red cells, 8.4 microns

A differential count showed polymorphonuclears, 75 per cent, lymphocytes, 20 per cent, eosinophils, 2 per cent, monocytes, 1 per cent, myelocytes, 1 per cent, and metamyelocytes, 1 per cent

The bleeding time was one and one-half minutes (Duke's method) and the coagulation time fifteen minutes (Lee and White) There was normal retraction of the clot Study of the fragility of the erythrocytes showed that hemolysis began in 0.4 per cent solution of sodium chloride and was complete in 0.3 per cent solution The plasma cell ratio was 77:23 The corrected sedimentation rate was 21 mm per minute

Course—The disease continued to run an afebrile course. The patient's only complaint was of pain on movement. One rarefied area in the ninth rib on the right side became painful and tender on pressure. On September 3 a portion of this rib was removed for biopsy.

Biopsy—Examination of the tissue removed from the ninth rib showed that the normal marrow was replaced by large and small cells, present in about equal numbers and having the same morphologic characteristics. (a) The large cells were round or oval, measuring from 10 to 18 microns in diameter, with an

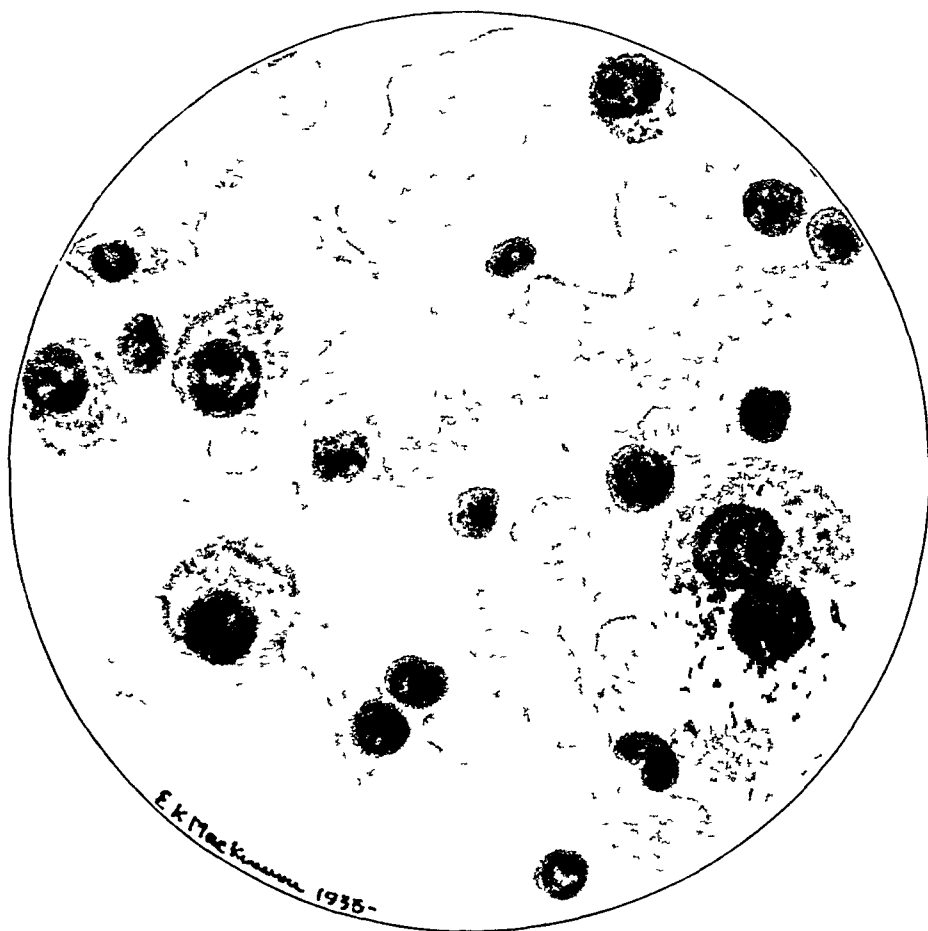


Fig 1—Camera lucida drawing of an actual field from a bone marrow smear, showing large and small plasma-like tumor cells. Their sizes may be compared with the size of the erythrocytes.

eccentrically placed hyperchromatic nucleus and nongranular, deep blue protoplasm. A number of these cells had two or three nuclei. Mitotic figures were present. (b) The smaller cells presented the same morphologic characteristics. Neither type of cell contained oxidase. Osteoclasts, many with inclusion bodies, were fairly numerous. No normal marrow tissue was present (figs 1 and 2).

From October 11 to 25 the urine contained a large amount of coagulable protein, which partially disappeared at a temperature above 56 C and reappeared on cooling below this temperature. However, during the last week of life the urine was entirely free from coagulable protein.

The patient rapidly became asthenic and died of bronchopneumonia on November 17

Autopsy—No lesions were noted except as hereafter outlined

The lungs showed bilateral hypostatic bronchopneumonia

The kidneys were of normal size, but the parenchyma was creamv pink, with a waxy appearance Amyloid was not present Microscopically, the femurs, the ribs, the vertebrae, the pelvic bones and, to a lesser extent, the skull showed extensive replacement of the medulla by islands of reddish gray tumor cells, similar to those described in the biopsy report These islands averaged 1 cm in diameter, although in places adjacent islands coalesced and formed larger tumor areas The cortex of the long bones was not invaded

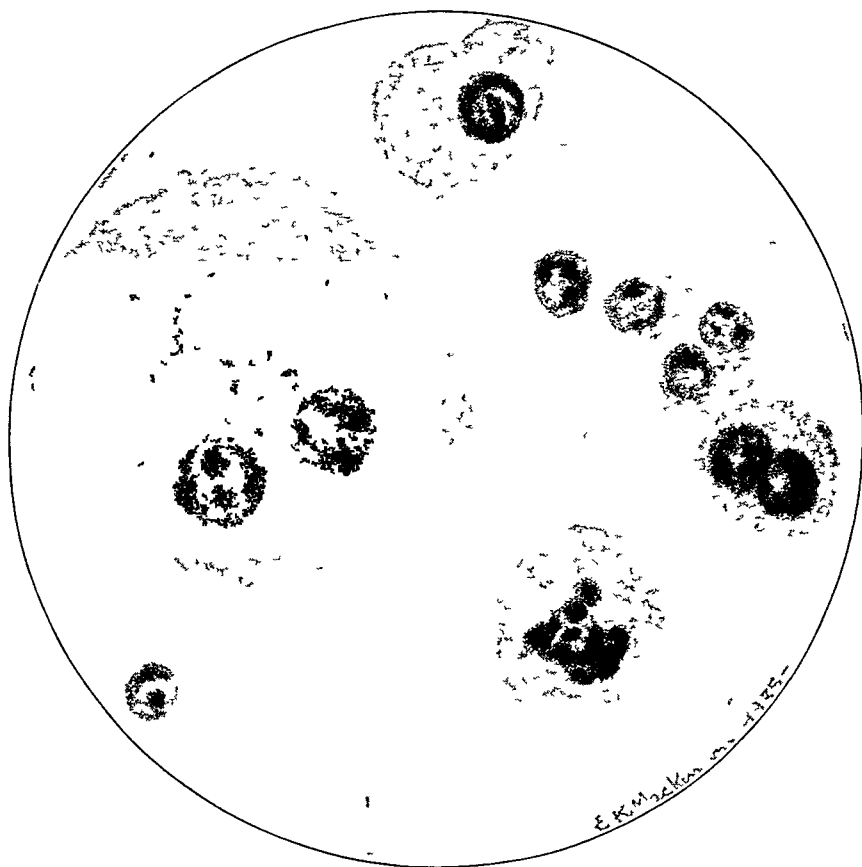


Fig 2—Another field from the smear shown in figure 1 The giant cell is believed to be an osteoclast

CASE 2—E H, a man aged 37, was admitted to the Montreal General Hospital, in the service of Dr L C Montgomery, on Sept 9, 1934, complaining of pain in the right thigh of one year's duration and generalized weakness

Personal History—The patient was a Canadian physician, single, who enjoyed excellent health until 1933, when he contracted pneumonia He had suffered since boyhood from periodic attacks of migraine, occurring about once a year

History of Present Illness—The patient enjoyed good health until December 1933, when atypical bilateral pneumonia (*Streptococcus nonhaemolyticus*) developed

followed by phlebitis of the left saphenous vein. He recovered slowly from this infection and remained in fairly good health until March 1934, when, after exposure, he had a second attack of pneumonia, localized in the base of the left lung and also followed by phlebitis of the right leg. The second attack of phlebitis persisted until July. Pain in the anterior aspect of the right thigh continued, however, and because of this he was admitted to the hospital.

Physical Examination—The temperature was 98.2 F, the pulse rate 116 and the respiratory rate 20. The patient was well developed and well nourished, with a good color. The eyes, ears, throat and thyroid gland were all normal. There was no adenopathy. The lungs were clear, except for pleural thickening at the base of the right lung. The heart was not enlarged, no murmurs were noted. The blood pressure was 124 systolic and 88 diastolic. The abdomen and genito-urinary system presented no abnormality. Examination of the right leg and thigh revealed only atrophy of the quadriceps muscle, with some limitation in the right hip to flexion and abduction. No tenderness of the skull or ribs was noted.

Laboratory Data—Urine. The urine showed good specific gravity. No sugar was present. There was 1+ albumin. Microscopically there was no blood or pus. Casts were found on one occasion (Sept. 15). Bence-Jones protein was never present (five tests).

Specimens of urine collected on September 20 and 21 showed a faint opalescence at 40 C, increasing at 60 C. No clearing occurred on further heating. The filtrate at 98 C was clear and remained so when cooled to room temperature.

Blood. On September 11 examination showed red blood cells, 3,600,000, white blood cells, 5,100, hemoglobin, 77 per cent (Hellige), diameter of red cells, 7.6 microns, and platelets, 274,000. The van den Bergh test showed 0.2 units.

A differential count showed polymorphonuclears, 51 per cent, lymphocytes, 43 per cent, monocytes, 3 per cent, and eosinophils, 3 per cent.

The bleeding and coagulation times were normal. There was no tendency to excessive clotting or the formation of rouleaux.

Chemical study of the blood showed urea nitrogen, 11 mg, creatinine, 1.67 mg, uric acid, 3.88 mg, cholesterol, 211 mg, and sugar, 114 mg, per hundred cubic centimeters. No Bence-Jones protein was present. On September 17 there was 5.8 mg of calcium and on September 20 11.9 mg. On September 17 there was 3.65 mg of phosphorus and on September 20 3.09 mg. There were 8.9 units of plasma phosphatase (Kay's method). The plasma proteins (Kjeldahl method) showed total protein, 12.39 Gm, albumin, 3.22 Gm, globulin, 6.58 Gm, and fibrinogen, 2.59 Gm, per hundred cubic centimeters.

Spinal Fluid. The spinal fluid showed a normal pressure. The total protein content was 0.04 Gm per hundred cubic centimeters. The Wassermann reaction was negative. The colloidal gold curve was normal.

Metabolism. The basal metabolic rate was -7.

Roentgenograms. Roentgenograms were made of the skull, spine, ribs, pelvis and femurs. Through all the bones were innumerable irregular areas of osteoporosis, most extensive in the right pubic bone, the descending ramus of which was completely destroyed.

Diagnosis—The diagnosis was multiple myeloma.

Clinical Course—On October 1, a 5 inch (12.7 cm) portion of the ninth right rib was removed with the patient under local anesthesia. The excised rib showed two localized tumor nodules, partially encapsulated and surrounded by areas of bone showing dissolution of trabeculae. The tumor nodules were composed of

fairly large round cells with pale-staining cytoplasm and a large vesicular eccentrically placed nucleus. Mitotic figures were fairly numerous. Although most of the cells were nongranular, a small proportion contained neutrophilic and eosinophilic granules.

During the succeeding month the patient complained of severe pain in the lower portion of the back. He became progressively weaker and died on November 3.

Autopsy—Postmortem examination showed terminal bronchopneumonia, with old pleural adhesions at the base and infarction of the middle lobe of the right lung. There was also thrombosis involving the inferior vena cava and renal veins, with recent infarction of both kidneys. Microscopic examination of sections from all parenchymatous organs showed no evidence of tumor. Sections from the skull, vertebrae, pelvis, femur and ribs showed involvement of the bone by tumor, with destruction of osseous tissue about the tumor areas. The character of the tumor corresponded closely with that given in the biopsy report. Sections of the kidneys showed massive recent infarction with patchy tubular degeneration. A few tubules contained albuminous casts. The interstitial tissue was infiltrated by foci of lymphocytes.

CASE 3—R. L., a soldier aged 26, single, was admitted to the Montreal General Hospital on Feb. 2, 1934, complaining of weakness, fever, loss of weight and pains in the back, neck, right leg and chest.

Family History—The family history was irrelevant.

Personal History—The patient was born in Montreal. He had never had any previous serious illness. He said he did not use alcohol but used tobacco moderately. He stated that he had not had a venereal disease.

History of Present Illness—The patient was perfectly well until November 1933, when he awoke one morning with diarrhea and aching pains in the loins and lower lumbar region. After several days the symptoms disappeared, and he returned to work. At the end of December he suffered a recurrence of the pains in the lower part of the back and loins. After taking to bed on December 29 he experienced similar pain in the neck, in the right leg and behind the sternum. During the interval from December 29, until his admission to the hospital on Feb. 2, 1934, the course was rapidly downhill, the patient showing progressive weakness and loss of weight. His temperature varied from 99 to 102 F.

Examination—The temperature was 101.2 F, the pulse rate 144 and the respiratory rate 20. The patient was a small, thin, pale man who looked ill. He held his head rigidly, owing to pain in the neck and back on movement. The eyes (including the fundi), ears, nose, throat and glandular system were not remarkable. The lungs were clear. The heart showed some enlargement to the right. There was a slight basal systolic murmur. The blood pressure was 124 systolic and 60 diastolic.

Examination of the abdomen, rectum, nervous system and genito-urinary tract revealed no abnormality. Tenderness was elicited over the chondrosternal junctions over the sternum and over the great trochanters but not elsewhere.

Laboratory Data—Urine. Twenty-three specimens of urine were examined. The specific gravity was consistently low (1.002 to 1.012), sugar was never present and albumin was present in amounts varying from a trace to 1+. Microscopically a little pus was present in all specimens but no blood, and on five occasions there was a rare granular cast. Bence-Jones protein was never present.

Blood The data on the blood were as follows

	Feb 2	Feb 7	Feb 22	March 3	March 31	April 25
Red blood cells, millions	2.2	1.86	1.27	1.94	1.81	1.67
Hemoglobin, %	36	30	25	38		30
White blood cells	17,600	7,450	11,050	6,800	7,800	19,850
Platelets, thousands		150	151	93		68
Reticulocytes, %		7.9	12.5			7.6
Polymorphonuclears, %	86	76	73	65	85	82
Lymphocytes, %	7	12	14	28	5	7
Eosinophils, %	0	5		1		1
Monocytes, %	4		3	2	1	0
Metamyelocytes, %		3	8			3
Myelocytes, %	2		2	2	2	3
Degenerates, %		4				4
Diameter of erythrocytes, microns		7.7	7.1			7.7

No Bence-Jones protein was present in the blood serum. Further chemical study showed urea nitrogen 17 mg, calcium, 14.7 mg, on February 8 and 9.9 mg on March 21, phosphorus 2.43 mg, cholesterol, 173 mg, plasma protein, 6.23 Gm, albumin, 3.99 Gm, globulin 1.61 Gm, and fibrinogen, 0.63 Gm per hundred cubic centimeters.

Electrocardiogram Abnormal ST waves indicated myocardial changes.

Wassermann Tests The Wassermann reaction of the blood and of the spinal fluid was negative.

Roentgenograms Roentgenograms were made of the pelvis, femurs, ribs and cervical, dorsal and lumbar regions of the spine. These showed destructive lesions involving the vertebral bodies, the ribs, the pelvic bones and the femurs suggestive of metastatic carcinoma.

Diagnosis—The first diagnosis considered was streptococcic septicemia. After the roentgenographic report had been given a complete clinical and laboratory investigation was undertaken to determine a possible primary malignant process, but none was found. The diagnosis of multiple myeloma was arrived at by a process of exclusion.

Clinical Course—The patient continued to fail progressively from the time of his admission to the hospital on February 2 until his death on April 27. His temperature showed a daily elevation as high as 103 F occasionally. Morphine was required daily for the pain in the neck and the lower part of the back. Toward the end of March pressure paraplegia developed at the level of the fifth thoracic segment. General anasarca appeared. Shortly before death occurred large bluish elevated swellings appeared in many of the costal cartilages and at the costochondral junction of the twelfth rib.

Autopsy—Postmortem examination revealed generalized anemia. No notable abnormalities were seen in the parenchymatous organs, except the slight cloudy swelling and mild inflammatory reaction of polymorphonuclear cells about the basophilic cellular debris in the tubules. The kidneys weighed 130 and 135 Gm respectively. The lesions in the bones were extensive, the sternum and bodies of the four lumbar vertebrae being almost entirely destroyed. In general, the histologic appearance resembled that in the crest of the left ilium, which was as follows. Only small patches of bony tissue remained. Surrounding and replacing these were solid masses of cells of two chief varieties: (1) large oval cells, having a pale hysochromic vesicular nongranular cytoplasm and an eccentrically placed large nucleus containing a central nucleolus, and (2) small cells differing from the larger cells chiefly in magnitude. Many large syncytial cells were also present. These were multinucleate and were considered to be osteoclasts. The only site of tumor, other than that in the long bones, was in the retroperitoneal glands near the pancreas and in the bifurcation of the aorta, which showed replacement by

tumor tissue of a type similar to that in the bones. In the midthoracic region was an area of complete absorption of the vertebral body, with involvement of cartilage, fibrous tissue proliferation and pressure involvement of the spinal cord.

CASE 4—R. M., a Canadian man of 69 years, was admitted to the service of Dr. C. P. Howard on October 9, 1935, complaining of renal and thoracic difficulties.

Family History—The family history was irrelevant.

Personal History—The patient was born in Quebec and worked as a farmer and sawmill operator. He was single, had never had venereal disease and had not used alcohol or tobacco to excess. He had never been ill until the onset of the present illness, except for typhoid when he was a young man.

Present Illness—The patient had enjoyed good health until two years before admission to the hospital, when he first began to complain of pain in the lower part of the back after any heavy lifting. For a month he had vomited frequently after meals. He had also had a great deal of pain in the right side of his back. He had had nocturia (urinating three or four times per night) for many years. During the past month he has been confined to bed because he was too weak to walk.

Examination—The temperature was 102 F, the pulse rate 108 and the respiratory rate 24. The patient appeared thin and sallow. The breathing was irregular and grunting, owing to substernal pain. The mental state seemed somewhat clouded. The left pupil was larger than the right and reacted sluggishly to light and in accommodation. Coarse moist râles were present throughout the lungs, and there was dulness in both axillae. The heart was slightly enlarged to the left. The blood pressure was 144 systolic and 60 diastolic. Many of the ribs were tender posteriorly, particularly on the left side. The abdomen was normal. The tendon reflexes were all present and normal.

Laboratory Data—Urine. The urine showed a heavy precipitate of coagulable protein on heating. This protein disappeared on further heating and reappeared on cooling to 56 C. This reaction was entirely reversible. The urinary sediment showed a few cellular and granular casts.

Blood Examination of the blood showed red cells, 3,500,000, leukocytes, 2,300, hemoglobin, 67 per cent (Hellige), platelets, 208,000, erythrocytic diameter, 79 microns, reticulocytes, 0.5 per cent, polymorphonuclears, 83 per cent, lymphocytes, 16 per cent, and monocytes, 1 per cent. The myeloid cells were nearly all immature polymorphonuclear cells. They showed basophilic degeneration of the granules but were not basophils. The Wassermann reaction was negative.

Chemical study of the blood showed urea nitrogen, 31 mg, creatinine, 3.26 mg, sugar, 164 mg, cholesterol, 129 mg, uric acid, 31 mg, phosphorus, 5.26 mg, calcium, 14.8 mg, total protein, 7.7 Gm, albumin, 5.04 Gm, globulin, 1.06 Gm, and fibrinogen, 1.6 Gm. The van den Bergh test showed 1 unit.

Electrocardiograms—Electrocardiograms showed a prolonged conduction time.

Roentgenograms—Roentgenographic study of the ribs, the vertebrae, the bones of the shoulder girdle, the pelvis and the femurs revealed discrete and confluent circular areas of destruction, most numerous in the ribs, many of which showed pathologic fractures.

Diagnosis—The diagnosis was multiple myeloma.

Clinical Course—The patient died of acute bronchopneumonia on October 12, three days after admission to the hospital.

Autopsy—Postmortem examination revealed generalized advanced arteriosclerosis, pneumonia of the lower lobe of the left lung, passive congestion of the lungs and liver and multiple osseous tumors. The kidneys weighed 150 and 200 Gm,

respectively. Microscopically the parenchymatous tissue showed marked degenerative changes. Many of the glomeruli were hyalinized. The tubular epithelia showed degeneration, with granular and hyaline casts filling the lumens of the tubules. No productive changes were present in the stroma.

TABLE 1—Data for Four Patients with Multiple Myeloma

	Case 1	Case 2	Case 3	Case 4
Age at onset	42 years	37 years	26 years	69 years
Sex	Male	Male	Male	Male
Duration of illness	4 months	11 months	5 months	24 months
Presenting symptoms				
Pains in lower part of back	Present, 3 wk	Not present	Present, 3 mo	Present, 2 yr
Pains in legs	Absent	Present	Absent	Absent
Weakness	Present, 4 mo	Present, 11 mo	Present, 5 mo	Present, 2 yr
General osseous pain	Absent	Absent	Present	Absent
Condition on admission				
Emaciation	None	None	Present	Present
Cachexia	None	None	Present	Present
Pallor	None	None	Present	Present
Pain on movement	Lumbosacral	Right hip	Head and extremities	Ribs
Urine				
Albumin	Trace, 7 or 15 tests	1— at times	Trace to 1+	1—
Casts	Once	Once	Rare, 5 times	Many
Sugar	Never	Never	Never	Never
Bence Jones protein	Never	Never	Never	Present
Proteose unidentified	Present	Never	Never	None
Blood				
Anemia	Hypochromic, moderate	Hypochromic, moderate	Hypochromic, moderate	Hypochromic, moderate
Leukocytes	Normal at first, later increased	Normal	Normal at first, later increased	Leukopenia
Platelet count	Low	Normal	Low	Normal
Differential count	Normal	Normal	Myelocytes, 2.5%	Normal
Van den Bergh test	Normal	Normal	Normal	Normal
Sedimentation rate	Very rapid	Rapid	Not tested	Not tested
Chemical study of blood				
Uric acid	High	Normal	Normal	Normal
Total protein	High	High	Normal	Normal
Albumin globulin ratio	Complete reversal	Complete reversal	Normal	Globulin low
Bence Jones protein	Absent	Absent	Absent	Not tested
Calcium	High	Low, then high	High, then low	High
Phosphorus	Normal	Normal	Normal	High
Involvement of bone (roentgen evidence)				
Spine	Present	Present	Present	Present
Pelvis	Present	Present	Present	Present
Ribs	Present	Present	Present	Present
Skull	Present	Present	Not studied	Not studied
Femurs	Present	Present	Present	Present
Tibias	None	None	Not studied	None
Humerus	None	None	Not studied	Present
Lung	None	None	None	None
Postmortem data				
Lungs	Terminal pneumonia	Terminal pneumonia, infarction of lung	Congested	Pneumonia
Liver	Normal	Normal	Normal	Congested
Spleen	Normal	Normal	Normal	Congested
Kidneys	Normal	Infarction	Swelling, degeneration	Hyaline degeneration
Type of lesion in bones	Typical	Typical	Typical	Typical
Retroperitoneal glands	No tumor	No tumor	Tumor present	No tumor

Sections of the sternum, pelvis, spine, skull, ribs and sphenoid bone were examined. All except the skull showed replacement of the marrow by islands of tumor tissue. The marrow of the sternum, ribs, vertebrae and pelvic bones was largely replaced by tumor tissue. Microscopically this tumor tissue consisted of large and

small plasma-like cells with large eccentric nuclei and nongranular basochromic protoplasm. Many of the cells contained nucleoli, and some were multinucleate. Osteoclasts were not numerous. The tumor cells all showed a negative reaction for oxidase.

COMMENT

The following summary of the data for our four patients shows certain interesting and unusual features, although none of these is foreign to the literature of the disease.

Age and Sex—Multiple myeloma is a disease of later life. Only five instances have been reported in which the patient was less than 35 years old, and for two of the patients there was no microscopic proof of myeloma, as noted by Geschickter and Copeland¹ in their comprehensive monograph. The ages of the patients who were shown to have myeloma were 30, 27 and 22 years, respectively. One of our four patients was 26 years of age, and the second was only 37. All four were men.

Etiology—Careful scrutiny of the clinical histories of our patients failed to reveal pertinent information relative to the etiology of the disease. The first patient was a Negro laborer born in British Guiana. The other three were native-born Canadians, one was a professional soldier, one a physician and one a farmer and sawmill operator. The Negro laborer had latent syphilis, but this disease had been successfully treated and at the time of his admission to the hospital the Wassermann reaction of the blood was negative. The family history did not record relevant facts. A history of trauma was not elicited in any of the cases.

Clinical Features—The duration of the illness from the onset of symptoms until death was four, five and eleven months, respectively, for the younger patients but somewhat longer for the 69 year old patient. The outstanding clinical symptoms on entry, in common with those of the vast majority of patients with the disease, were pain and weakness. The pain occurred in the lower lumbar or sacral region of the back in three of the four patients and in the lower extremities in two, but generalized osseous pain was noted in only one. Weakness was an outstanding symptom, having been present in these patients even before the onset of the pain. Sharp accentuations of pain and periods of remission were noted by three of the four patients. Severe pain on movement was noted by all four. In one instance its site was the lumbosacral region, in a second, the right hip, in a third, the head and extremities, and in the fourth, the ribs.

Physical examination of the patients in all instances revealed surprisingly little information so far as diagnostic features were concerned. Perhaps the pain in the back and weakness should have suggested the

¹ Geschickter, C. F., and Copeland, M. M. Multiple Myeloma, Arch. Surg. 16: 807 (April) 1928.

possibility of this disease to the clinician, but invariably it was the roentgenogram which pointed to the correct diagnosis. None of the patients when first observed had sufficient osseous destruction to produce deformity, pathologic fracture or even egg-shell crackling, although two patients eventually showed tumors of the ribs and sustained pathologic fractures. Pressure paraplegia was a terminal complication in one patient. The blood pressure was always within normal limits.

Laboratory Data—The urine of only one of the four patients showed Bence-Jones protein, although the other three patients were under observation for long periods and many urinalyses were made. In the urine of one patient (case 1) an unidentified proteose was observed on several occasions. Albumin, casts and blood cells were not more frequently found than would be expected in any progressive malignant process. At no time were there sufficient urinary findings to suggest the presence of nephritis.

The examination of the blood showed moderate anemia in all cases. In the first patient it was of the hyperchromic type, with definite macrocytosis, the modal erythrocyte having a diameter of 8.4 microns. In the other three patients the anemia was of the hypochromic type. In two patients the leukocytes were normal at first, but moderate leukocytosis developed later. The fourth patient had terminal leukopenia. The differential count was within normal limits for three patients. The third patient occasionally showed 2 or 3 per cent myelocytes. The platelet counts were normal for two patients and low for the other two. The sedimentation rate was rapid in one.

In summary it may be stated that the hemogram failed to show any characteristic feature. Emphasis is placed on the absence of immature myeloid cells in all but one patient, although many studies were made. This finding is counter to the prevalent opinion, although actual statistics show that only one patient in four shows myelocytes in the peripheral blood.

Chemical study of the blood revealed that one of the unusual, though not unique, features in two of the patients was hyperproteinemia. This increase in the plasma protein content was due, in both instances, to an increase in the globulin content. In the second patient an increase in the fibrinogen content also occurred. In contrast to the increased globulin content, the albumin content was reduced to approximately half the usual value. No determination of the osmotic pressure of the plasma was made, but tissue edema did not occur. Consequently it may be assumed that the osmotic pressure of the plasma was not greatly reduced. The hyperglobulinemia probably compensated in part for the lack of serum albumin. It was of further interest that the only patient who showed Bence-Jones protein had neither hyperproteinemia nor hyperglobulinemia. None of the patients showed abnormally rapid coagulation or a

tendency to rouleaux formation, although the thrombophlebitis in the third patient was suggestive. In fact, the first patient showed a slight prolongation of the coagulation time (Lee and White method). However, the corrected sedimentation rate (Ernstene and Rourke method) was 21 mm per minute, an unusually high figure. The occurrence of hyperproteinemia in multiple myeloma is infrequent, as determined from a study of the literature up to 1935. Sweigert² was able to collect reports of only sixteen instances of hyperproteinemia prior to his own, in approximately five hundred reports of cases of the disease, although he was able to find reports of only thirty-five cases of multiple myeloma in which a satisfactory quantitative investigation of the plasma proteins had been made. The presence of an unidentified proteose in the urine and blood plasma, as in our first patient, has been considered by some authors³ to possess the same diagnostic significance as Bence-Jones protein. In the reports of cases of hyperproteinemia in multiple myeloma the excessive quantities of protein have been said to be either some form

TABLE 2—Data on Plasma Proteins

	Case 1	Case 2	Case 3	Case 4
Total proteins, Gm per 100 cc	12.58	12.39	6.23	7.70
Serum albumin, Gm per 100 cc	2.36	3.22	3.99	5.04
Serum globulin, Gm per 100 cc	9.96	6.58	1.61	1.06
Fibrinogen, Gm per 100 cc	0.26	2.59	0.63	1.60
Bence Jones protein	Absent	Absent	Absent	Present
Unidentified proteose	Present	Absent	Absent	Absent

of globulin or actual Bence-Jones protein. In only one instance (the patient reported on by Reimann⁴) was an excess of fibrinogen found. Our second patient was therefore almost unique in this respect, showing an excessive amount both of globulin and of fibrinogen. Table 2 is a summary of the plasma protein values for our four patients.

Course of the Disease—All four patients eventually revealed the progressive changes common to all forms of malignant disease. The third patient had a high fever for many weeks. The spine, bones of the pelvis, femurs and ribs of all the patients were extensively involved. Roentgenograms of the skull were not made in two cases, but those for the first and second patients showed typical lesions. The immediate cause

2 Sweigert, C. F. Multiple Myeloma with Hyperproteinemia, *Am J M Sc* **190** 245, 1935.

3 Rosenblum, A. H., and Kirshbaum, J. D. Multiple Myelomas with Tumor-Like Amyloidosis. A Clinical and Pathologic Study, *J A M A* **106** 988 (March 21) 1936.

4 Reimann, H. A. Hyperproteinemia as a Cause of Autohemagglutination. Observations in a Case of Myeloma, *J A M A* **99** 1411 (Oct 22) 1932.

of death in three of the four patients was pneumonia. Infarction of the lung and the kidneys of the second patient was also noted post mortem.

Autopsy—The postmortem data may be separated into two groups: those regarding the lesions in the bones and those regarding the parenchymatous organs, in a measure secondary to the tumor itself.

(a) Pathologic changes not directly due to the tumor were present in the lungs and in the kidneys. Three of the four patients showed a terminal bronchopneumonic process. The second patient had saphenous and femoral thrombophlebitis which extended into the inferior vena cava and involved both renal veins. There was also infarction of the middle lobe of the right lung, probably secondary to the thrombotic process in the inferior vena cava. The renal lesions were of interest because nephritis has been frequently reported in this disease. Geschickter and Copeland⁵ observed nephritis of the nephrosis type in about 60 per cent of one hundred and fifty patients. Ninety-two patients had nephritis and Bence-Jones protein; thirty-seven had nephritis alone and in only five were both nephritis and Bence-Jones protein absent. These data suggest some connection between the proteinuria and the lesions in the kidney. Bell, on the other hand, concluded from a study of eleven patients that renal insufficiency in multiple myeloma is due in a majority of instances to vascular degeneration, pyelonephritis incident to "cord bladder" or prostatic hypertrophy.

Renal insufficiency was not a feature in any of our four patients, although our second patient had terminal infarction of both kidneys. The kidneys of the first patient were normal. Mild degenerative changes were present in the kidneys of the third and fourth patients, although only one patient had Bence-Jones proteinuria. These data support the contention that proteinuria is not an important cause of the tubular degeneration.

(b) The tumor as observed in biopsy sections and post mortem presented all the gross and microscopic features characteristic of multiple myeloma of the plasma cell type. The tumor cells of all four patients presented a similar histologic appearance. They resembled plasma cells only in shape and in the eccentric position of the nucleus. Otherwise they presented the characteristics of a rapidly proliferating neoplasm. Mitotic figures and large multinucleated cells were numerous. The accompanying camera lucida drawings of actual fields in the biopsy specimens from the first patient illustrate the histologic features of the tumor cells. The large cell with inclusion bodies is an osteoclast, not a tumor cell. Metastases to parenchymatous organs or lymphatic vessels were searched for but observed only in the third patient, who showed

⁵ Bell, E. T. Renal Lesions Associated with Multiple Myeloma, *Am J Path* 9: 393, 1933.

involvement of the retroperitoneal glands. Direct extension of the tumor from the vertebrae seemed unlikely, as the involved glands were not contiguous to the invaded bone.

SUMMARY

Four patients with multiple myeloma of the plasma-like cell type were studied by clinical and laboratory methods and eventually subjected to complete postmortem examination. The first patient was admitted because of pain in the lower part of the back of three weeks' duration, but he had worked with pick and shovel the day prior to admission to the hospital. The disease was considered to be arthritis associated with chronic gleet until a roentgenogram showed lesions suggestive of multiple myeloma. Moderate hyperchromic anemia, hyperglobulinemia and an unidentified proteose in the blood and urine were noted. The patient died of bronchopneumonia one month after admission to the hospital.

The second patient was hospitalized because of pain in the thigh following two attacks of pneumonia complicated by phlebitis. The diagnosis was again suggested by the appearance of the roentgenograms. There were moderate hypochromic anemia and hyperfibrinogenemia as well as hyperglobulinemia. Death followed thrombosis of the inferior vena cava, with infarction of both kidneys and a portion of the right lung. The tendency to venous thrombosis in the presence of hyperproteinemia is recognized and may have been an important factor, although no change in the coagulability of the blood was noted.

The third patient was admitted because of generalized osseous pain, high fever, severe anemia and leukocytosis. A tentative diagnosis of atypical subleukemic myelosis or streptococcic septicemia was made. The diagnosis ultimately rested between carcinomatosis and multiple myeloma. The problem was finally settled by biopsy of a tumor in one rib. No changes in the blood proteins were found. The disease eventually caused pressure paraplegia, and there was metastasis to the retroperitoneal lymph nodes.

The fourth patient, the only one to show the Bence-Jones protein, was an old man who was admitted because of bronchopneumonia. He had been in failing health for a month, although he had had pain in the back for two years. The diagnosis of multiple myeloma was suggested when the urine was examined and later was confirmed by roentgenograms of the spine and pelvis. The blood showed moderate anemia but no hyperproteinemia.

It is evident from a study of these four patients that multiple myeloma of the plasma cell type may or may not be accompanied with changes in the plasma proteins or with the appearance of proteose or Bence-Jones proteinuria and further that these changes, when present bear no definite relation to degenerative changes in the kidney.

CONCLUSIONS

Weakness and pains in the lower portion of the back are the most constant symptoms of multiple myeloma

Frequently no characteristic clinical signs and symptoms are noted until the disease is far advanced, although the combination of weakness, persistent pain in the back and anemia is suggestive of the disease

The diagnosis can usually be made roentgenographically on the basis of the punched-out areas of rarefaction in the pelvic bones, vertebrae or skull

The presence of Bence-Jones protein or some type of proteose in the blood and urine is of diagnostic value, but many patients with the disease show neither

Hyperglobulinemia with or without an increase in the fibrinogen content is probably more common than a survey of the literature indicates and may predispose to venous thrombosis

Anemia is almost always present, it may be severe and either hyperchromic or hypochromic

Metastases are unusual but may occur to the retroperitoneal glands

Clinically evidence of degenerative changes in the kidneys is often lacking or insignificant

SIGNIFICANCE OF HEMOLYTIC STREPTOCOCCIC BACTEREMIA

A STUDY OF TWO HUNDRED AND FORTY-SIX PATIENTS

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The prognosis in infection due to hemolytic streptococci depends on the summation of such factors as the age of the patient, the location and type of the infection, the presence or absence of debilitating disease and bacteremia. For several years we have been interested in assessing the relative importance of these various factors in hemolytic streptococcic infection. At present we are reporting the results of a study of 246 patients with hemolytic streptococcic bacteremia, together with some of our observations concerning the variation in the organisms producing these infections and the defense mechanism of the host.

In general, bacteremia may be interpreted as due to a loss of equilibrium between the normal clearing mechanism of the body and the local defense mechanism. In the case of hemolytic streptococcic bacteremia there are reasons for believing that bacteremia results from the invasive properties of this particular species of organism and differences in the defense mechanism of the host.

ANALYSIS OF CASES

Seasonal Incidence—As might be anticipated, the highest incidence of bacteremia was observed during the months when hemolytic streptococcic infections are most prevalent, that is, from January to May.

Age of the Patients—The age distribution for patients with bacteremia fell into three distinct groups. The first, representing the patients in the first two decades of life, included most of the patients with bacteremia arising from infections of the throat and middle ear, including lateral sinus thrombosis, cavernous sinus thrombosis and thrombophlebitis of the deep tonsillar veins. The second group included

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the patients with puerperal infections most of whom were observed between the ages of 20 and 40 years. Finally, the third group was made up of patients with cellulitis, most of whom were over 40 years of age. This distribution is shown in chart 1.

Mortality According to Age Distribution and Portal of Entry—The relation of the incidence and fatality rate to these two factors is shown in charts 2 and 3. From chart 2 it may be seen that the fatality rate definitely increases with age and, while it is high in all decades, it is particularly noticeable that for patients over the age of 20 the number of deaths increases. When the three major groups are studied separately as shown in chart 3, it is seen that the increasing fatality not only varies with the age of the patient but with the localization of the primary infection. It was lowest for the patients with

TABLE 1—Type of Infections

	Total Number of Cases	Total Number of Total Cases	Fatality, Percentage
Primary infections			
Infections of throat, middle ear and mastoid, including thrombosis of lateral sinus, cavernous sinus and tonsillar vein	69	38	55
Pelvic infections	41	25	76
Cellulitis and erysipelas	61	49	80
Streptococcal infections secondary to			
Pneumonia	18	15	83
Diabetes	10	9	90
Tuberculosis	6	5	83
Operative treatment	22	20	90
Arteriosclerosis	19	18	95
Total	246	177	72

infections of the throat, middle ear and mastoid during the first two decades of life, while it was highest in all age periods for patients with cellulitis and erysipelas. The total fatality rate is given in table 1, this has been presented regardless of the ages of the patients. Here again, it is plain that the highest mortality occurred among patients with cellulitis and erysipelas and those with debilitating diseases, whereas for the other infections the percentage of fatality was lower.

Focal Lesions—One of the characteristic features of hemolytic streptococcal infection with bacteremia is the relative infrequency of metastatic lesions in the form of abscesses. This series of patients was no exception to that well recognized fact. The various metastatic lesions which were observed are listed in table 2. The commonest suppurative lesions were in the joints, the subcutaneous tissues and the endocardium. Miscellaneous features are also listed in table 2. They comprise a large group but, on the whole, were infrequent. Sixty-two per cent of all the patients showed no metastatic lesions. The comparatively small number of patients with focal lesions is probably due, in part at least,

TOTAL
CASES

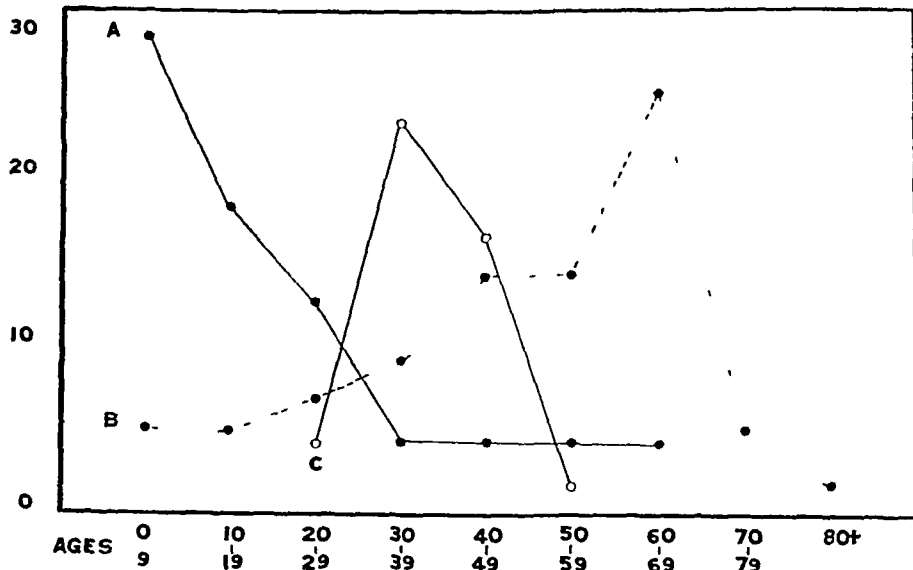


Chart 1—Age distribution for patients with bacteremia according to the portal of entry *A* indicates infections of the throat, middle ear and mastoid, *B*, erysipelas and cellulitis, *C*, puerperal sepsis

TOTAL
CASES
FATALITY
%

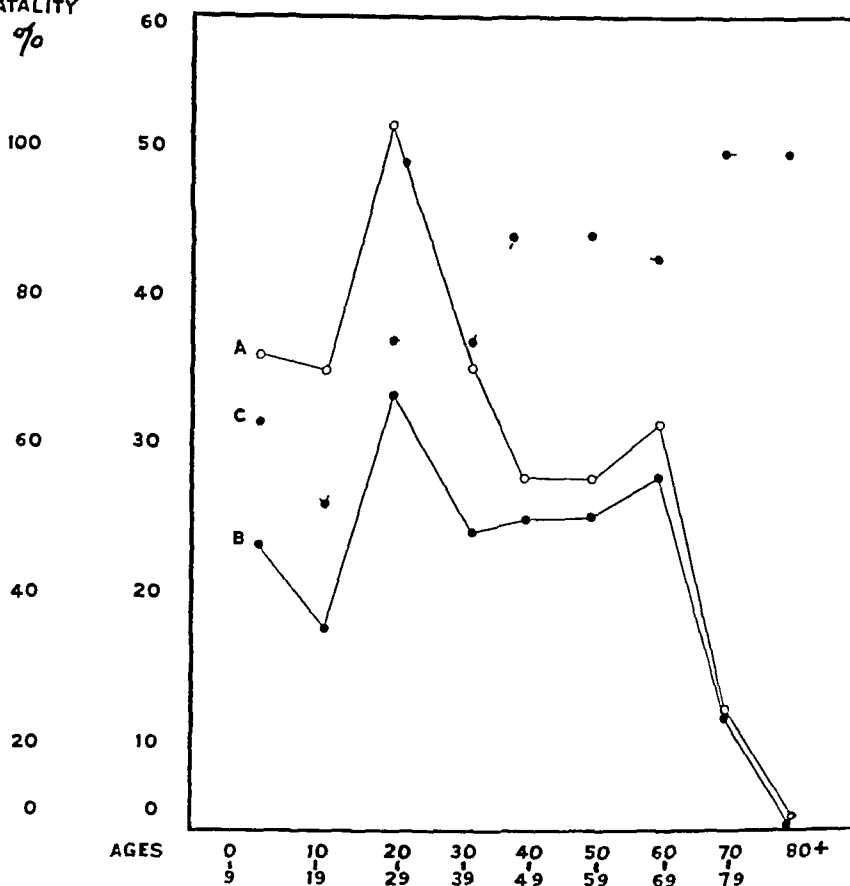


Chart 2—Age distribution of patients with bacteremia, the total number of patients of each decade who died and the percentage of deaths for each decade *A* indicates the total number of patients in each decade, *B*, the number of patients who died, and *C*, the percentage of deaths in each decade

to the rapid course of the infection, together with the character of the infecting organism, as it produces substances which dissolve fibrin, kills leukocytes and in this way prevents the local defense mechanism

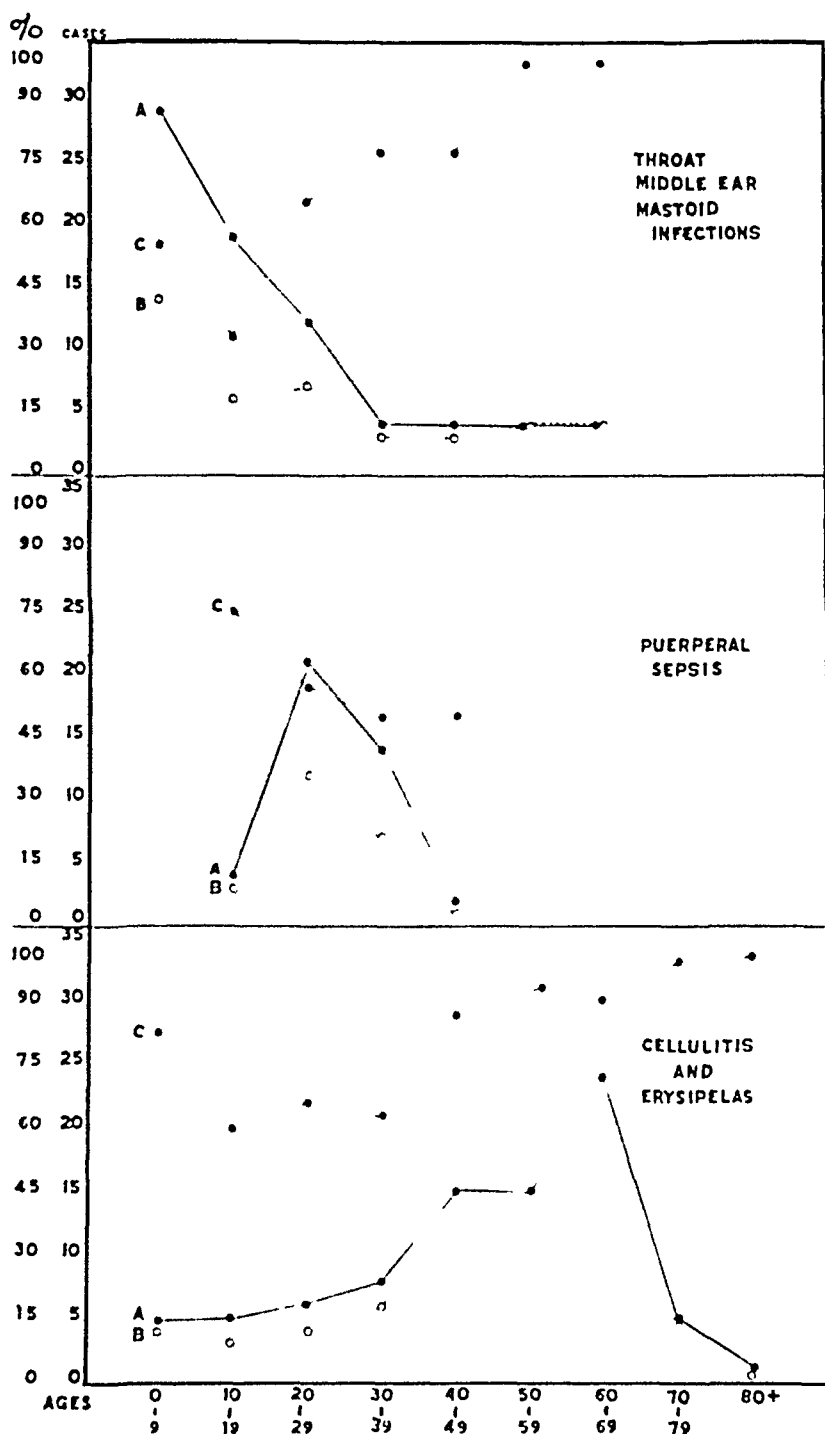


Chart 3—The total number of patients with bacteremia arising from various foci of infection in different decades of life, together with the total number and the percentage of deaths in each decade. *A* indicates the total number of patients, *B* the total number who died, and *C*, the percentage of deaths.

from becoming effective and fully operative. In table 3 the duration of the illness in patients with bacteremia is summarized. In the majority of patients the illness was of relatively short duration. Those surviving longer than from twenty to thirty days usually have focal lesions which gradually subside spontaneously or after the surgical drainage of an abscess. In chart 4 the data for a group of patients has been charted, showing the rapidly progressing type of sepsis, with fatal outcome within a few days. In chart 5 it may be seen that for other patients who show bacteremia at the beginning of the illness, if the blood stream

TABLE 2—*Mortality Statistics*

	Total Number of Cases	Number of Recoveries	Number of Deaths
Metastatic lesions			
Arthritis	49	20	29
Subcutaneous abscesses	17	7	10
Endocarditis	11	0	11
Osteomyelitis	4	2	2
Abscess of lung	3	0	3
Empyema	5	2	3
Miscellaneous lesions			
Nephritis	4	0	4
Jaundice	7	0	7
Peritonitis	7	0	7
Abscess of spleen	1	0	1
Agranulocytosis	3	0	3
Mediastinitis	2	0	2
Meningitis	3	0	3
None	153	39	114

TABLE 3—*Duration of Illness*

Duration of Illness, Days	Number of Fatalities	Number of Recoveries
Less than 10	85	19
11-20	49	11
21-30	23	9
31-40	4	3
41-50	9	8
51+	7	19
Total	177	69

is cleared of organisms and if focal abscesses develop and can be treated surgically, recovery takes place. In chart 6 data for a group of patients are recorded showing temporary bacteremia, clearing of the blood stream without focal infection in all but 2 patients and recovery.

The charts show that the following sequence of events may occur. First, there may be a temporary invasion of the blood, with rapid clearing, no metastases and recovery. Second, after the bacteremia the blood may be cleared of organisms, and focal metastases may be set up in various areas, usually the joints, subcutaneous tissues or other organs. The outcome may be favorable if the abscesses can be drained adequately by surgical procedures, or a fatal outcome may result if the

abscesses are widespread and cannot be effectively treated. Finally, there may be rapidly progressive bacteremia without focal lesions, death resulting within a relatively short time.

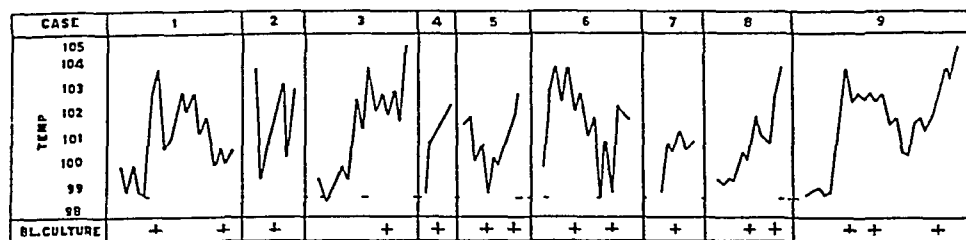


Chart 4—Temperatures (F) of patients with rapidly progressing bacteremia without localization. The arrow indicates the time of parturition in a patient in whom peritonitis developed.

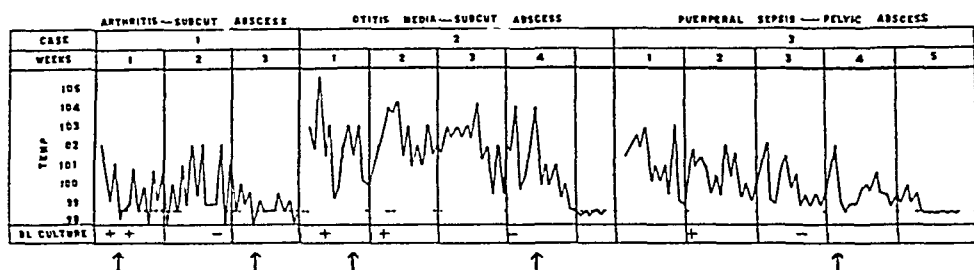


Chart 5—The course of hemolytic streptococcic infection with bacteremia in 3 patients. The bacteremia was followed by clearing of the blood stream and abscess formation. Recovery followed drainage of abscesses. The arrows indicate the drainage of the abscesses.

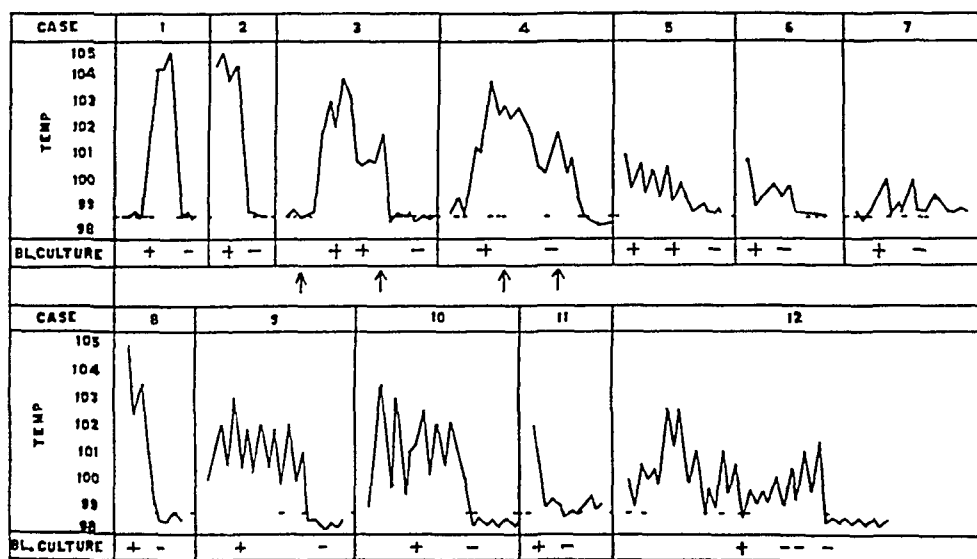


Chart 6—Temperatures of patients with hemolytic streptococcic bacteremia for whom culture of the blood was made. Death occurred in 9. The blood was cleared promptly in all but 2 patients without abscess formation. The arrows indicate the time of incision of an abscess.

CHARACTERISTICS OF THE ORGANISMS CAUSING BACTEREMIA

To supplement the clinical observations and to obtain more information concerning the mechanism of bacteremia, we studied a small group of patients with hemolytic streptococcic bacteremia and compared the findings with those for a group of patients with hemolytic streptococcic infections without bacteremia. This study was concerned with the characteristics of the organisms and the immune response of patients with local and general infections.

In 8 patients with bacteremia it was found that the organisms all belonged to group A of Lancefield, and they were all beta hemolytic streptococci. Fibrinolysin and erythrogenic toxin were produced by all the strains, and they were all M strains, according to the classification of Ward and Lyons¹. These organisms were not typed, because typing serum was not available.

To determine the capacity of these organisms to resist phagocytosis in normal blood, bactericidal tests with whole blood were made. It was ascertained that only one of the eight strains was phagocytosed and killed in moderate degree by normal blood. While this is not a particularly good method of testing the relative virulence of the various strains of hemolytic streptococci, it serves as a test that can be used for normal persons and for patients with infections in order to determine the bactericidal power of the whole blood against homologous as well as heterologous strains of hemolytic streptococci.

When these results were compared with those obtained from a study of the bactericidal power of the same controls with the organisms isolated from patients with local lesions without bacteremia, it was found that the blood of control subjects was capable of killing a number of the strains which were isolated from local lesions. These observations can be taken as an indication of the variation in the bactericidal power of the blood of normal persons for various strains of hemolytic streptococci, the blood of some healthy persons is capable of killing varying numbers of virulent hemolytic streptococci in vitro.

BACTERICIDAL POWER OF BLOOD OF PATIENTS WITH BACTEREMIA

When micro-organisms are growing rapidly in one or more foci of infection and overflowing into the blood faster than the clearing mechanism can eliminate them, bacteremia follows. At present it is generally believed that the most important groups of cells in removing organisms from the circulating blood are the cells of the reticulo-endothelial system. Moreover, it is well known that the efficiency of these cells in

¹ Ward, H., and Lyons, C. Studies on the Hemolytic Streptococcus of Human Origin. I. Observations on the Virulent, Attenuated and Avirulent Variants. *J. Exper. Med.* **61** 515, 1935.

removing bacteria from the circulating blood and preventing secondary waves of bacteremia can be enhanced by introducing specific antibodies into the circulating blood or by a process of conditioning these cells through the previous immunization of the animal. That these cells can remove bacteria from the circulating blood while it is not possible to demonstrate the presence of antibodies has been amply demonstrated by Teale². It also has been clearly shown by McMaster and Hudack³ that antibodies develop locally in some tissues and in a higher concentration than exists in the circulating blood. It follows then that it is possible for the blood to be cleared of bacteria so that even specific antibodies cannot be demonstrated therein. However, it was of some interest to us to test the blood of patients with bacteremia for antibodies and compare the results with those for patients with local lesions without bacteremia.

TABLE 4—*Bactericidal Power of the Blood of Eight Patients with Hemolytic Streptococcic Bacteremia*^{*}

Case	Maximum Number of Organisms Killed by 0.5 Cc. of Blood		Outcome	Disease
	Cases	Controls		
1	10 ⁻⁴	10 ⁻⁷	L	Erysipelas
2	10 ⁻⁴	10 ⁻⁷	L	Pneumonia and empyema
3	10 ⁻⁴	10 ⁻⁷	L	Puerperal sepsis
4	10 ⁻⁷	10 ⁻⁷	D	Puerperal sepsis
5	10 ⁻⁴	10 ⁻⁷	D	Thrombophlebitis of jugular vein
6	10 ⁻²	10 ⁻⁴	D	Postoperative sepsis with multiple abscesses
7	10 ⁻²	10 ⁻⁷	L	Recurrent erysipelas
8	10 ⁻¹	10 ⁻⁷	D	Puerperal sepsis with multiple abscesses

* 10⁻⁷ indicates from 2 to 10 organisms per 0.1 cc., L, living, and D, died.

The methods for studying the bactericidal power were the same as previously reported⁴. The results of the study are recorded in table 4. Seven of the 8 patients with streptococcic bacteremia had antibodies,

2 Teale, F. H. Some Observations on the Relative Importance of the Reticulo-Endothelial Tissues and the Circulating Antibody in Immunity. I. Bacterial Immunity in Relation to the Role Played by the Circulating Antibody and the Tissues Following Intravenous Introduction of the Bacteria, *J. Immunol.* **28** 133, 1935. II. Hypersensitiveness and Immunity to Foreign Proteins. An Analysis of the Parts Played by the Tissues and Circulating Antibody in These Two States, *ibid.* **28** 161, 1935. Some Observations on the Question of the Various Manifestations of Antibody Activity Being Due to Separate Antibodies or an Immune Substance Acting Differently Under Various Conditions, *ibid.* **28** 241, 1935.

3 McMaster, P., and Hudack, S. S. The Formation of Agglutinins Within Lymph Nodes, *J. Exper. Med.* **61** 783, 1935.

4 Spink, W. W., and Keefer, C. S. Studies of Hemolytic Streptococcal Infection. II. The Serological Reactions of the Blood During Erysipelas, *J. Clin. Investigation* **15** 21, 1936.

when the local defense mechanism is ruptured. This is illustrated in chart 7. A young woman with a chronic sinus in one axilla had recurrent erysipelas of the thoracic wall after surgical incision of the sinus. With the onset of erysipelas, bacteremia occurred. This was transitory, and at the time of this observation antibodies were demonstrated in the circulating blood. The second attack of erysipelas was accompanied with bacteremia and followed surgical incision of the sinus. The third and fourth febrile attacks shown in the chart were due to an intercurrent attack of acute tonsillitis and a final attack of erysipelas without bacteremia. It seems clear then that the blood stream may be invaded even when antibodies are present, but under these conditions the blood is often rapidly cleared of organisms.

BACTERICIDAL POWER OF BLOOD OF PATIENTS WITH LOCAL LESIONS

It has been postulated that local infections caused by hemolytic streptococci are due (1) to infection with an organism of such low virulence

TABLE 5—*Maximum Number of Hemolytic Streptococci Killed by 0.5 Cc of Blood from Patients with Local Lesions Without Bacteremia*

Dilution of Organisms*	Total Number of Cases	Total Number of Controls
10 ⁻¹	18	4
10 ⁻²	3	3
10 ⁻⁴	1	5
10 ⁻⁶	0	8
10 ⁻⁷	0	2
Total	22	22

* 10⁻⁷ indicates from 2 to 7 organisms per 0.1 cc

that it can be phagocytosed by normal blood⁵ or (2) to the presence of an increase in the local and general resistance of the host for the particular infecting strain of bacteria, so that the spread of the infection is prevented. In other words, it has been suggested by one group of investigators that local infections are due to organisms of relatively low virulence, whereas those which invade the blood stream are of higher virulence. Another group maintains that it is a matter of the general resistance, as determined by the immune response of the patient. In regard to these questions there is no agreement, since the methods available for measuring the virulence of an organism are unsatisfactory and the results are difficult to interpret. It is now known that the blood of some normal persons is capable of phagocytosing and destroying hemolytic streptococci which have been isolated from the circulating blood, and it can be demonstrated that some normal persons are unable to phagocytose and destroy organisms that are derived from local lesions. These findings have been reported previously,⁴ but for purposes of comparison they are summarized in table 5.

All the patients with local lesions could be shown to possess the capacity of destroying varying numbers of the homologous organisms, and this property of the whole blood increased during the course of the disease. The blood of normal controls did not contain antibodies for all strains of organisms, but antibodies for some strains were present. Here again it was not possible to say that the localized infection was due to the presence of antibodies prior to the onset of the disease, since none of the patients was studied before the initial attack. However, we have observed persons who have had recurrent attacks of erysipelas and who have had a good antibody titer in the blood preceding the attack.

As a whole, the evidence suggests that patients with local lesions without bacteremia have antibodies against the homologous organism, and these antibodies increase during the course of the disease. While it is possible for bacteremia to take place even when antibodies are present, these antibodies undoubtedly play a part in limiting the invasion of the blood and assist in the localization of the infection.

In summary it may be said that hemolytic streptococci that produce local or general infection in man belong to group A of Lancefield, they are strongly hemolytic and produce fibrinolysin and other toxic substances.

Patients with local hemolytic streptococcal infections have demonstrable antibodies in the blood, and the titer of these antibodies increases during the course of the disease. This property probably explains in part the reason for the localized infection. The presence of antibodies in the blood does not completely protect a person from a local infection or from bacteremia, since bacteremia may occur when there are antibodies present in the circulating blood if the local defense mechanism is ruptured by trauma or surgical interference. Furthermore, it can be demonstrated that patients with rapidly progressive infection may have no antibodies in the blood, whereas those that survive and in whom foci of infection develop invariably show antibodies. It has been stated by Hare¹ that at least half the patients who die of hemolytic streptococcal infections have antibodies in the circulating blood, and we have been able to confirm this observation. Three of our 4 patients who died (table 4) had demonstrable antibodies in the circulating blood. In 3 of the 4 the blood had been cleared of bacteria, but the patients died of multiple abscesses or of a local infection that could not be treated surgically. It does not seem unreasonable to suppose therefore that recovery from hemolytic streptococcal infection with bacteremia depends on the development of an effective local and general defense mechanism and that this depends in large part on a high grade of immunity and on the location of the infection.

MECHANISM OF BACTEREMIA

As has been stated, bacteremia may be considered to be the result of a loss of equilibrium between the normal clearing mechanism and the rapid overflow of bacteria from one or more foci of infection. It follows that the presence of bacteria in the blood will depend on the balance of these two factors. That is to say, when organisms are growing rapidly and overflowing into the blood faster than the clearing mechanism can eliminate them, bacteremia will follow. Or, when there is an overflow of organisms from a focus or foci of infection when the clearing mechanism has ceased to operate or is functioning at a low level of efficiency, bacteremia will result. Hemolytic streptococci are among the most invasive organisms producing disease. This invasiveness depends on the type of streptococci and the degree of general or local resistance of the tissues. In regard to the invasive qualities of the organism, certain facts have been gained by a number of investigators which aid in understanding this property. It is known that only a certain group of hemolytic streptococci are capable of producing disease in man and of invading the blood stream. This group includes the so-called group A or virulent human strains, according to the classification of Lancefield.⁶ Tillett and Garner⁷ have demonstrated that these organisms are capable of producing fibrinolysin, which is a substance that is capable of dissolving fibrin and perhaps of preventing the fixation of organisms locally at the site of invasion. Menkin⁸ has marshalled evidence to show that hemolytic streptococci are unable to produce substances that injure tissues in such a way as to produce lymphatic thrombosis, and as a result the organisms can spread and grow freely in the lymphatic vessels draining a focus of infection. Ward and Lyons,¹ Hare⁵ and others have shown that invasiveness depends in part on the ability of the organisms to resist phagocytosis. This property, in turn, depends on the type of variant, the capsular substance or the so-called opsonogenic substance of the organism. Undoubtedly other aggressive factors about which little is known at present may aid the organisms in invading the tissues. These are various toxic substances elaborated by the organisms, such as leukosidins and erythrogenic toxin. In any event, it is evident that this group of organisms is capable of producing chemical substances which enhance their free growth in tissues and invasion of the circulating blood.

6 Lancefield, R. C. A Serological Differentiation of Human and Other Groups of Hemolytic Streptococci, *J. Exper. Med.* **57** 571, 1933.

7 Tillett, W. S., and Garner, R. L. The Fibrinolytic Activity of Hemolytic Streptococci, *J. Exper. Med.* **58** 485, 1933.

8 Menkin, V. Inflammation and Bacterial Invasiveness. *Am. J. M. Sc.* **190** 583, 1935.

SUMMARY

From the clinical study of the 246 patients with bacteremia the following facts were elicited

Bacteremia in hemolytic streptococcal infection is seen most often in patients in the first, fourth and seventh decades. These peaks of incidence correspond to the age incidence of infections of the throat and middle ear, the puerperal infections, and cellulitis and erysipelas.

The general fatality rate was 72 per cent. It was highest for the patients with cellulitis and erysipelas regardless of age, slightly lower for those with puerperal sepsis and lowest of all for patients less than 20 years of age with infections of the throat, middle ear and mastoid. Aside from the differences in mortality according to age and portal of entry, such factors as the duration of the sepsis, the location of infection in an area that could or could not be treated adequately and the presence or absence of debilitating diseases were of importance in determining the outcome.

The commonest metastatic lesions were in the joints, subcutaneous tissues and endocardium, although only about 30 per cent of the patients showed metastases.

Recovery following bacteremia occurred after a transitory invasion of the blood from a focal lesion without metastases or when the blood stream was cleared of organisms and focal infection was established if the lesion could be treated surgically.

Death occurred among those with debilitating diseases, those with rapidly spreading infection without localization and those in whom localization occurred in an area which could not be treated surgically (peritoneum, endocardium or meninges). Sometimes the blood was cleared of organisms, but the foci of infection were situated so that they could not be treated adequately.

From a study of the organisms which cause bacteremia and the immune reactions of patients with and without bacteremia the following statements are justified.

Organisms isolated from local lesions and from the circulating blood were beta hemolytic streptococci. They all belonged to group A of Lancefield, and they all produced fibrinolysin.

Organisms isolated from the circulating blood frequently resisted phagocytosis and were not killed by blood from normal persons. There are exceptions to this observation, but, by and large, it is true.

Organisms isolated from local lesions were phagocytosed by the leukocytes of some normal persons and killed in varying numbers by those of different persons. The blood of patients with local lesions usually possesses the capacity of killing the homologous organisms and

this function increases with the course of the disease. The presence of circulating antibodies assists in localizing the infection and in preventing bacteremia.

In patients with bacteremia antibodies develop which aid in the clearing of the blood stream. In our experience all the patients with bacteremia who recovered had demonstrable antibodies in the circulating blood, and it was shown that antibodies were present in some of the patients who died, although the titer was low.

Bacteremia in hemolytic streptococcic infection is of greater value in prognosis than in diagnosis, and its presence may be taken as an indication of a loss of equilibrium between the local defense mechanism and the normal clearing mechanism. The presence of specific antibodies plays an important part in preventing bacteremia and in clearing the blood of organisms once it has become invaded by organisms from the local focus.

Progress in Internal Medicine

REVIEW OF NEUROPSYCHIATRY FOR 1937

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Many papers are written on psychiatry every year but few deal with treatment. This year is an exception. Two new therapeutic methods have come into prominence, one has been discussed largely in the public press under the inexcusable name psychosurgery, and the other has caused a flood of literature in the medical press—the insulin shock treatment of schizophrenia.

“PSYCHOSURGERY”

Moniz, a Portuguese neurologist, well known for his studies on cerebral arteriography, and his colleague Lima¹ tried to alter by cerebral surgery the mental symptoms of twenty persons suffering from different psychoses, the condition presented by ten of these would probably be classified in America as severe agitated depression, three were manic and seven were schizophrenic. All those suffering from depression were improved by interruption of tracts in the frontal lobe, the results in the two other groups were dubious. In America Freeman² has taken up this work and reports on a small series of cases. His method is to introduce a ‘leucotome’ through a small trephine hole and cut the white matter of the frontal lobe. (He calls it the prefrontal area, but how can an area be in front of the front?) With this instrument several balls of white matter are cut away from their connections and left in place. The operation is done blindly, and hemostasis is impossible. Thorium is injected into the hole afterward to show just where the white fibers were cut. As a rule from three to six lesions are made in each frontal lobe. In some cases of severe agitated depression there was a remarkable change. The patient became calm and less tense, and the mood improved conspicuously. In such cases this radical treatment occasionally seems justifiable. The patient is old, he is intensely unhappy and the prognosis is bad. Freeman, however, reports treating in this way patients with neuroses and young persons with schizophrenia. This mutilation of

1 Moniz, E, and Lima, A. *Premiers essais de psycho-chirurgie. Technique et resultats*, Lisboa med **13** 152-161, 1936

2 Freeman, W, and Watts, J W. *Prefrontal Lobotomy in the Treatment of Mental Disorders*, South M J **30** 23-31, 1937 .

the brains of patients who might recover seems to me unjustifiable. Not only does "leucotomy" leave a necrotic mass of tissue and hemorrhage that may well cause cicatrix and epilepsy later, but thorium is a radioactive substance that may harmfully affect distant parts of the brain. Whatever the demerits of the procedure may be, it is an interesting physiologic observation that cutting off certain tracts beneath the frontal cortex will make a patient more placid. Somewhat analogous results have been obtained in monkeys by Jacobsen³

THE TREATMENT OF SCHIZOPHRENIA BY INSULIN HYPOGLYCEMIA

Dementia praecox, or schizophrenia, as it is now generally called, is the most devastating of the major psychoses, both from the standpoint of bad prognosis and from that of economic waste, for it is a common disease, often starts early in life and may run a course of twenty or even forty years. The etiology is unknown, but there is good evidence that the disease runs in families⁴ (i e., that the seed is bad) and that environment plays a great rôle in developing the symptoms⁵ (i e., the soil is poor). These persons seem to be born tender, they are exquisitely vulnerable to the hurts of the world. Those with most marked involvement seem to deteriorate steadily, with little or no stimulus from the environment, those with mild involvement live relatively acceptable lives if they can be protected from the buffets of the world. The symptomatology can be roughly summed up as a withdrawal from reality into a world of fantasy. Until recently treatment has been largely symptomatic, and a few patients have been treated by psychologic means by those with much time and inexhaustible patience. But, on the whole, results have been disappointing and confused by the fact that from 25 to 30 per cent of the young patients have a long remission that may look like cure and a considerable number have one brief episode and regain a fairly normal equilibrium lasting for the remainder of life. In patients in whom the disease has run a course of several years, the chance of spontaneous remission falls to 5 or 10 per cent. For such a scourge, the victims of which occupy nearly two hundred thousand hospital beds in the United States, it is natural that any new treatment should be welcomed by members of the medical profession.

3 Jacobsen, C. F., and Nissen, H. W. Studies of Cerebral Function in Primates. Effects of Frontal Lobe Lesions on Delayed Alternation Habit in Monkeys, *J. Comp. Psychol.* **23** 101-112, 1937.

4 Cobb, S. Review of Neurology and Psychiatry for 1935-1936, *Arch. Int. Med.* **58** 1111-1123 (Dec.) 1936.

5 Sullivan, H. S. Environmental Factors in Etiology and Course Under Treatment of Schizophrenia, *M. J. & Rec.* **133** 19-22, 1931.

It has long been known that any situation which brings a schizophrenic patient near death may rid him temporarily of his mental symptoms. Burrows,⁶ in 1828, recommended camphor in large doses to produce fits and cure "insanity," but he warned that in rash hands it may be dangerous to life.

In a case of insanity, where two scruples were exhibited, it produced a fit, and a perfect cure followed. When given to the same gentleman two years afterwards, upon a relapse, i. e., a recurrence, it had the same effect, even to an alarming degree, but the patient did not, as before, progressively recover from a single dose, for it was repeated afterwards in smaller doses of ten grains.⁷

In like manner, major operations (if really major enough) for the "removal of foci of infection" or any other cause have been followed by remissions in mental symptoms, sometimes fairly long remissions and frequently short ones. Witness the colectomies performed about fifteen years ago on many inmates of hospitals for patients with mental disease. Moreover, it is an old story to psychiatrists that the occurrence of a severe infectious illness in a schizophrenic patient may cause the mental symptoms to disappear for a time. Inducing in these patients convulsions with metrazol⁸ has had a similar effect, and periods of hyperpnea induced by breathing carbon dioxide and oxygen have brought about brief lucid intervals.⁹ Most recently insulin hypoglycemia has taken the field. The only factor common to these different procedures is a severe metabolic change. It has been argued that the effective mechanism common to these different shocks may be psychologic—the schizophrenic patient is faced with a state of biologic urgency, often actually a fear of death. This state of terror is first induced and then relieved by a physician, and a new emotional situation is brought about. It can equally well be argued that some unknown chemical changes in the nerve cells are common to all these states, but it must be a basic change if caused by so many and such varied procedures.

The discovery by Manfred Sakel, of Vienna, that severe and repeated insulin hypoglycemia causes remission in many cases of schizophrenia has aroused great interest. His first publication appeared in

6 Burrows, G. Commentaries on the Causes, Forms, Symptoms, and Treatment, Moral and Medical, of Insanity, London, Thomas & George Underwood, 1828.

7 Dr. Diethelm, of New York, gave me this interesting reference.

8 Meduna, L. Versuche über die biologische Beeinflussung des Ablaufes der Schizophrenie, Campher und Cardiazolkrämpfe, *Ztschr. f. d. ges. Neurol. u. Psychiat.* **152** 235-262, 1935.

9 d'Elseaux, F. C., and Solomon, H. C. Use of Carbon Dioxide Mixtures in Stupors Occurring in Psychoses, *Arch. Neurol. & Psychiat.* **29** 213-230 (Feb.) 1933.

November 1934,¹⁰ and reports from him and others corroborating the observations have followed fast (The most important references¹¹ give a thorough review of the subject)

Technic of Treatment—In Sakel's own words, given in a recent paper,¹² the technic is as follows

The technique requires that the patient be given increasing doses of insulin until the so-called shock dose is reached, the size of the shock dose varies considerably in different individuals and may be anything from 15 to 450 units. The initial dose varies from 15 to 50 a day depending on the physical condition of the patient and the duration of his illness, and the doses are increased by 5 to 20 units daily until the shock dose is reached.

By shock dose we understand that amount of insulin which in any individual produces deep coma with areflexia within four or five hours after one injection.

A shock dose is given three to six times a week until the desired result is attained, but if the patient does not respond no more than 50 injections need be given.

at least one to three days of rest are allowed every week.

The insulin injection is always given fasting and is followed in four or five hours by a sufficient amount of carbohydrates.

The neurological symptoms of hypoglycemia or coma are not dependent on any one blood sugar level.

Individual variations have to be made continuously, as therapeutic results cannot be achieved by a stereotyped repetition of hypoglycemic states measured by so many hours, but depends instead on the correct management of each individual hypoglycemic state, and especially on its termination at the right moment. These are matters which can be learned only through long experience.

The therapeutic aim is to find a dose and a time of termination of hypoglycemic symptoms which will produce the most desirable clinical

10 Sakel, M. Schizophreniebehandlung mittels Insulin Hypoglykämie sowie hypoglykämischer Schocks. *Wien med Wchnschr* **84** 1211 (Nov 3), 1265 (Nov 17), 1299 (Nov 24), 1326 (Dec 1), 1353 (Dec 8), 1383 (Dec 15), 1401 (Dec 22) 1934, **85** 35 (Jan 5), 68 (Jan 12), 94 (Jan 19), 152 (Feb 2), 179 (Feb 9) 1935.

11 (a) Sakel¹⁰ (b) Dussik, K. T., nad Sakel, M. Ergebnisse der Hypoglykämieschockbehandlung der Schizophrenie, *Ztschr f d ges Neurol u Psychiat* **155** 351-415, 1936. (c) Wortis, J. On the Response of Schizophrenic Subjects to Hypoglycemic Insulin Shock, *J Nerv & Ment Dis* **84** 497-506, 1936. (d) Langfeldt, G. Die Insulin-Chokbehandlung der Schizophrenie, *Psychiat-neurol Wchnschr* **38** 483-484, 1936. (e) Friedlaender, K. Insulin-Chokbehandlung der Schizophrenie, *ibid* **38** 520, 1936. (f) Glueck, B. Hypoglycemic State in the Treatment of Schizophrenia, *J A M A* **107** 1029-1031 (Sept 26) 1936. (g) Berze, J. Die Insulin-Chok-Behandlung der Schizophrenie, *Wien med Wchnschr* **83** 1365-1369, 1933. (h) Benedek, L. Insulin-Schock-Wirkung auf die Wahrnehmung, Berlin, S. Karger, 1935. (i) Sakel, M. Neue Behandlungsmethode der Schizophrenie, Leipzig, Verlag M. Perles, 1935. (j) Wortis, J. Sakel's Hypoglycemic Insulin Treatment of Psychoses. History and Present Status, *J Nerv & Ment Dis* **85** 581-595, 1937. (k) Symposium on Therapy Including Hypoglycemia, *Am J Psychiat* **94** 89-208, 1937.

12 Sakel, M. The Methodical Use of Hypoglycemia in the Treatment of Psychoses, *Am J Psychiat* **94** 111-129, 1937.

results This may involve terminating at the end of an hour or so in the case of stupor, choosing as the time of termination the period when the patient is most responsive Or it may involve termination just before coma or within a few minutes of the institution of coma in the excited patient or termination after a long period of coma in the paranoid patient

The symptoms¹³ of insulin shock may be divided into four groups (a) The first group includes symptoms arising from the autonomic system—variation of pulse rate and blood pressure, drop in temperature, perspiration and salivation, pallor and flushing Of these, the drop in temperature and the perspiration are the most constant and therefore the best indication of shock (b) The motor symptoms start with restlessness and tremor, passing through various stages of twitching until pathologic reflexes appear At the end there may be convulsions ending in muscular flaccidity and coma with areflexia (c) The disturbances of consciousness start with sleepiness, then comes sleep from which the patient can be aroused, later he cannot be aroused and is in coma (d) The mental syndrome is variable—the excited patient may become composed, or the stuporous patient may go into a state of extreme excitement

The indications for terminating the treatment are deep coma with flaccidity, laryngospasm, generalized extensor rigidity of the muscles or severe convulsions, or tachycardia, Cheyne-Stokes respiration or a sudden fall in blood pressure late in coma In about 7 per cent of the cases of shock early termination is necessary for one of these reasons

Results of Treatment—In *Science* for June 25, 1937,¹⁴ the following statement is made "More than 1,000 mental cases have been restored to health and sanity by treatment with insulin" It is difficult to amass the data necessary to make up a statistical review, because many of the reports have been recently made at meetings and are not yet available in print Nevertheless, I feel that this statement was not justified In the first place, the number of patients who have remission early in the disease is variously estimated to be from 20 to 30 per cent Moreover, "restored to health and sanity" is phraseology not easily subjected to scientific analysis, and "full remission," "good remission" and "social recovery" apparently are not employed in the same way in the different clinics A report on the Vienna series by Dussik and Sakel^{11b} states that one hundred and four patients were treated The authors consider that fifty-eight of these had a good remission, but they

13 Potzl, O, Forstg, J P, and Muller, M Seminar on Insulin at Vienna University Psychiatric and Neurologic Clinic, 1937, to be published

14 Insulin in the Treatment of Schizophrenia, *Science* (supp) **85** 10 (June 25) 1937

divide their patients up into the new and the old ones. For the new ones (those who had had symptoms for only a year or less) there was a remission rate of 88 per cent, whereas for the old ones it was 48 per cent. Three died. Optimistic reports such as this are the ones quoted in the press, and they raise the hopes of many families. It is never emphasized sufficiently that a large percentage of the selected patients would have had a remission anyway and that remission is not cure.

The work in America is now actively under way, and preliminary reports were read at the meeting of the American Psychiatric Association in Pittsburgh last June. On the whole these are more conservative, but they are so recent that one cannot judge of their permanent value. Ross¹⁵ reports on thirty-eight patients, nineteen had returned home since treatment, nine of those who remained in the hospital were improved somewhat and ten were not improved at all. Katzenelbogen¹⁶ reports from the Phipps Clinic at Johns Hopkins Hospital on sixteen patients, six had a complete remission, and four showed moderate improvement. Wortis and his co-workers¹⁷ report on thirty schizophrenic patients treated during the last eight months, there was full remission in eleven, "social recovery" in eight, improvement in two and no improvement in nine. Young and his co-workers¹⁸ state that eighteen of their thirty-one patients had a good remission, thirteen showed "social recovery," seven were not improved and two died. As far as I can summarize the American figures that are available, they indicate that about half the patients treated (for the most part after careful selection) become well enough to return home for a time, as yet undetermined, and half obtain little or no benefit. About 15 or 20 per cent die. The results are obviously a good deal better than those obtained by the usual methods of hospitalization and general institutional care. In the hospitals where there are enough trained physicians to give careful individual attention to the patients' psychologic problems the results in cases of early involvement are much better than those in the hospitals where the care is merely custodial. But there are not enough patients treated in this way to make statistics available.

15 Ross, J. R. Report of the Hypoglycemic Treatment in New York State Hospitals, *Am J Psychiat* **94** 131-135, 1937.

16 Katzenelbogen, S., Harms, H., and Clark, D. A. Experience with the Hypoglycemic Treatment of Schizophrenia, *Am J Psychiat* **94** 135-152, 1937.

17 Wortis, J., Bowman, K. M., Orenstein, L. L., and Rosenbaum, I. J. Further Experiences at Bellevue Hospital with the Hypoglycemic Insulin Treatment of Schizophrenia, *Am J Psychiat* **94** 153-158, 1937.

18 Young, G. A., Young, R. H., and Roucek, L. Experiences with the Hypoglycemic Shock Treatment of Schizophrenia, *Am J Psychiat* **94** 159-170, 1937.

Apparently the results from convulsions and shock after metrazol treatment compare favorably with those from insulin shock ¹⁹

It is not, however, the number of cases of remission which is most impressive, it is the experience of the physicians who have watched these patients through treatment that makes one realize that something very radical is happening to the psyche. Wortis and his co-workers ¹⁷ say

Our patients grew calmer and more collected after their first injections, grew more lucid and accessible thereafter, and then began to show insight—at first during hypoglycemia and later throughout the day as treatment progressed. Some cases relapsed during treatment but were revived again and in all our cases we have had to fit our treatment to the individual and vary our procedure accordingly.

Physiology and Pathology—Whatever may be the ultimate outcome of insulin therapy, some important physiologic observations are being made on the patients. Hundreds of severe insulin shocks are being given to persons who are relatively normal except for their mental symptoms. Himwich and his colleagues ²⁰ have found that the oxygen utilization of the brain is greatly decreased during hypoglycemic coma (average before coma, 7.09 volumes per cent, during coma, 2.46 volumes per cent). When the oxygen utilization is definitely decreased the Babinski sign appears, when this condition is prolonged all reflexes are lost.

Experiments on animals by Kerr and Ghantus ²¹ show that overdosage with insulin causes a marked decrease in the glycogen content of the brain of dogs and rabbits, but this decrease in the brain is less marked and is later than the decrease in the sugar content of the blood. The lowering of the sugar content of the brain appears to be due to an increased utilization of carbohydrate in the brain itself, since the concentration of free sugar in the brain is constantly less than that in the blood. A secondary lowering of the sugar content of the brain could occur owing to insufficient supply from the blood. The disturbances of the central nervous system after insulin treatment are due to both factors—increased utilization and insufficient replacement.

¹⁹ Meduna, L. Die Konvulsionstherapie der Schizophrenie, *Psychiat-neurol Wchnschr* **37** 317-319, 1935. Meduna, L., and Gyárfás, K. Ueber die Cardiazol-Krampfbehandlung der Schizophrenie, *Arch f Psychiat* **106** 1-12, 1936. Janz, H. W. Die diagnostische Verwertbarkeit einiger Methoden zur Provokation epileptischer Anfälle, *ibid* **106** 267-295, 1937. Camp, W. J. R. Pharmacology of Metrazol, *J Pharmacol & Exper Therap* **33** 81-92, 1928. Flaum, E. Kritik der Kardiazolwirkung, *Klin Wchnschr* **14** 1543-1548, 1935.

²⁰ Himwich, H. E., Bowman, K. M., Wortis, J., and Fazekas, J. F. Brain Metabolism During the Hypoglycemic Treatment of Schizophrenia, *Science* **86** 271-272 (Sept. 17) 1937.

²¹ Kerr, S. E., and Ghantus, M. Carbohydrate Metabolism of Brain. Effect of Varying Carbohydrate and Insulin Supply on Glycogen, Free Sugar, and Lactic Acid in Mammalian Brain, *J Biol Chem* **116** 9-20, 1936.

The mechanism by which hypoglycemia may cause coma and convulsions is not known. There are some hints that it may be related to the action of neurohumors at nerve endings in the fact that dextrose inhibits the liberation of substances which sensitize tissues to the action of acetylcholine, a substance which inhibits certain convulsions²²

Another important line of investigation is the study of the "brain waves" during insulin hypoglycemia. Hoagland, Cameron and Rubin²³ have found that the encephalogram becomes broken up as hypoglycemia progresses, concurrently the alpha waves decrease in frequency per second and eventually disappear. As the patient comes out of coma the record becomes more even, and the alpha waves return. When muscular twitchings occur there are no waves such as appear in epileptic patients, the process is apparently electrically different. The variation in the number and in the size of large waves before and after insulin treatment may prove to be an important aid in controlling treatment.

Muller²⁴ has studied the symptoms of hypoglycemia exhibited by these patients and is most impressed by the fact that the actual amount of blood sugar seems to have little to do with the reactions. No symptoms appear unless the level of blood sugar drops to 60 mg per hundred cubic centimeters, but the level may fall below 30 mg before symptoms appear or they may be severe at levels only a little below 60 mg. These discrepancies may be due to differences in the method of collecting blood. Venous blood usually shows between 20 and 30 mg per hundred cubic centimeters during coma. The systolic blood pressure rises, and the diastolic pressure may fall. There is usually tachycardia, up to 100 or 120 beats per minute, and the patient feels a rapid, pounding heart. Slow pulse and falling blood pressure are late and dangerous signs. The electrocardiogram may show a flattened T wave.

The gross and microscopic changes that may be present in the brain after severe hypoglycemia are well described by Moersch and Kernohan²⁵. They performed autopsies on two persons who died of spontaneous hypoglycemia (hyperinsulinism). The lesions of this disease cannot be said to be identical with the cerebral changes following insulin shock, but physiologically and clinically the conditions have much in common. The brain of the first patient showed edema and widespread degeneration of the nerve cells in the cerebral cortex and diencephalon, with acute changes in the microglia and oligodendroglia. "There were

22 Gerard, R. W., in Luck, J. M. Annual Review of Biochemistry, Stanford University, California, Stanford University Press, 1937, vol. 6, p. 435.

23 Hoagland, H., Cameron, D. E., and Rubin, M. A. The Electroencephalogram of Schizophrenics During Insulin Treatments, *Am J Psychiat* **94** 183-208, 1937.

24 Muller, M., cited by Glueck^{11f}

25 Moersch, F. P., and Kernohan, J. W. Hypoglycemia. Neurologic and Neuropathologic Studies, *Arch Neurol & Psychiat*, to be published.

practically no normal nerve cells in the cerebral cortex" In certain devastated areas no nerve cells remained, and there was degeneration of the underlying white matter In the second case the histologic examination was less complete, but again there was a conspicuous loss of cells in the cerebral cortex and in the hindbrain, the tissue looked edematous and extravasation of red blood cells into perivascular spaces was noted Another autopsy, described by Vonderahe,²⁶ revealed diffuse degeneration throughout the brain, with especially marked lesions in the hypothalamus

Two cases have been reported in which cerebral hemorrhage followed the coma and convulsions of insulin treatment for schizophrenia At the meeting of the American Neurological Association Keyes, Freed and Riggs reported a case in which insulin treatment for schizophrenia caused a prolonged convulsion, during which hemorrhage took place into the subarachnoid space, accompanied with hemiparesis and prolonged stupor They observed petechial hemorrhages in the brains of five patients who died of hypoglycemia

Salm²⁷ reports a case in which the patient under treatment with insulin went into coma as usual, had severe convulsions and could not be aroused The temperature rose to 40 C, the pupils were small and unequal Death occurred on the eleventh day of coma Autopsy showed hemorrhage about the third ventricle of the brain and small extravasations of blood in the substantia nigra and vegetative nuclei In the cortex the nerve cells showed widespread degeneration such as is seen after asphyxia

Taking this evidence from microscopic observation and comparing it with the physiologic evidence that there is a marked lack of oxygen during the coma, it seems reasonable to conclude that asphyxia of the brain may play an important part in the phenomena of hypoglycemic coma and convulsions It also seems possible that severe insulin shock destroys a great number of cerebral nerve cells Some of the changes described are doubtless reversible, but experimental work on animals indicates that most asphyxiated nerve cells go on to permanent degeneration²⁸ Hemorrhages in the brains of animals after induced hypoglycemia from insulin are reported by two groups of workers²⁹ These were

26 Vonderahe, A R Personality Change in Hypoglycemia, *J Med* **17** 189-190, 1936

27 Salm, H Benommenheitszustände in Anschluss an die Insulinschockbehandlung von Schizophrenen, *München med Wchnschr* **84** 1047, 1937

28 Gildea, E, and Cobb, S The Effects of Anemia on the Cerebral Cortex of the Cat, *Arch Neurol & Psychiat* **23** 876-903 (May) 1930

29 Baker, A B, and Lufkin, N H Cerebral Lesions in Hypoglycemia, *Arch Path* **23** 190-201 (Feb) 1937 Steif, H, and Tokay, L Beiträge zur Histopathologie der experimentellen Insulinvergiftung, *Ztschr f d ges Neurol u Psychiat* **139** 434-461, 1932

usually in the basal ganglions but often in the cerebral cortex. A recent report by Schmid³⁰ that repeated hypoglycemic states cause no permanent lesions in the brain has been quoted by several protagonists of insulin treatment. This paper by Schmid, however, is a preliminary report on three guinea-pigs. One had fourteen and the other two only ten hypoglycemic periods each. The paper proves nothing. It must be granted, on the other hand, that most experimenters have given the animals more severe shocks than the schizophrenic human beings have received. Thus those authors³¹ who wish to be conservative and give pause to the enthusiastic insulin therapists emphasize the human autopsy reports just quoted, while the enthusiasts pass over them, saying that cerebral damage occurs only in fatal cases, that in therapy the process remains within physiologic limits, i. e., the cell changes are reversible, and the cell returns to normal. My opinion is that there probably is destruction of cerebral nerve cells during coma and convulsions. Both the physiologic and the pathologic reports suggest strongly to me the probability that the cerebrum is partially asphyxiated for long periods during treatment. But losing these nerve cells may be relatively harmless, no one knows how many cells may be lost without causing mental impairment. Certainly there is a great reserve that is probably not called on for ordinary mental activity, and perhaps many of the patients are considered in "good remission" when they are simply living along and not disturbing their neighbors.

Theoretical Considerations—Many of the writers on the insulin shock treatment of schizophrenia mention in passing the fact that here at last is a good chemical treatment for a mental disease, which proves that all this psychologic bosh was wrong. They do not use these words, but the implication is evident. It is to be deprecated that every first year student of medicine cannot be given a lecture on the logic of departmental relations in a medical school. He would then understand, once and for all (for I believe any one who can get into a good medical school has brains enough to see it), that anatomy, physiology and psychology are merely names for administrative departmental units, they are convenient pigeonholes to house the professors, but there is no scientific fact that makes a separation between the departments biologically reasonable. When Himwich²⁰ says "The ameliorations which occur must be ascribed to functional changes in the brain," he is saying nothing that is not entirely self-evident. The brain is the organ of mind, its function is the integration of nerve impulses, the most complex integrations being called mental. Any change in menta-

30 Schmid, H. Zur Histopathologie der Sakel'schen Hypoglykämieschockbehandlung der Schizophrenie, Schweiz med Wchnschr 66 960-961, 1936

31 Cobb, S. Shock Therapy, New England J Med 217 195-196, 1937

tion therefore involves "functional changes in the brain" Moreover, function is impossible without an organ that functions The lines drawn between "organic and functional," "physical and mental," are illusory and result from a harmful sort of academic thinking Regarding the problem of insulin shock, therefore, the psychologist may describe the behavior of the patient as he comes out of coma and may make use of his suggestible state of mind to change his thought content, the physiologist may determine the amount of sugar in the blood at various stages of the treatment, if the patient dies the anatomist will be interested in the petechial hemorrhages in the diencephalon or the degenerations in the cortical nerve cells Each investigator has his problem but in order to make progress each must know something of both of the other problems and must have respect for the workers and their data At a meeting last spring when Dr Sakel spoke, it was amazing to see the audience split up into two factions—the "organicists," whose attitude was "Here is proof at last that dementia praecox is an organic disease," and the "psychologists," who felt "Of course, nearly killing a man will change his mental content and bring him back to reality" No one seemed to realize that in biology it is never a question of *either* a functional or an organic problem but always a question of *both*

In a paper read at the meeting of the American Psychiatric Association on May 14, 1937, Sakel¹² discusses his theory of the action of hypoglycemia on the brain He is cautious and starts out by saying that the new treatment has no basis on biologic or physiologic principles such as scientific medicine usually demands Nevertheless, since this treatment has been hit upon by chance, he thinks it should be made use of, not only for empirical therapy but, by working backward, for the elucidation of the cause of schizophrenia itself This, he says, is difficult indeed, for "We know nothing either about the conditions or processes involved in normal thinking, to say nothing of the complicated processes that must be involved in an hallucination or delusion" (I applaud Sakel's caution, but I do not agree with his nihilism, I think there is a great deal of scientific data on all these subjects) Having thus washed the slate clean, he proceeds to describe his "working hypothesis," which he admits is schematic, but necessary for the development of the method and technic The nerve cell is compared to a "fuel engine" which has "excitant material" comparable to "fuel," normal "tonus" is kept up in the nerve cell by "the proportional mixture of excitant and inhibiting hormones" The nerve cell is said to have two "valences" which are "saturated with the excitant hormone in order to preserve a normal tonus" If the valences are abnormally saturated, "abnormal relaxation of the cell" may result

After reading two pages of this, my mind had a surrealistic picture of a gas-engine nerve cell with fuel, hormones, valences, tonus and

the power to relax. Since only contractile tissues and elastic bodies have the power to relax, the picture is not only confusing but preposterous. Such a naive mixture of physics, chemistry, physiology and circumlocution has rarely appeared in a medical journal. It is scientific hypothesis degenerating to mixed metaphor.¹

Sakel's explanation of why hallucinations and delusions disappear in hypoglycemic shock is equally fallacious. He postulates the thinking process on specialized and fixated "intracellular pathways," saying that "the youngest and most active pathways in the nervous system are the most sensitive to injury" and that "the special sensitivity of everything that is of more recent development, more complicated and more dominant," allows the hypoglycemia to stop the function of the pathways thus designated, sparing the others.

Nothing is known of "intracellular" pathways such as Sakel postulates. Dominant paths are often neither recent nor complex. It is not true that pathways of more recent development are as a rule more susceptible to injury than older ones. Noxious agents are known that strike selectively the older neurologic mechanisms and spare the newer—poliomyelitis affects the ventral horn cells of the cord, encephalitis lethargica the gray nuclei of the brain stem and methyl alcohol the optic nerves, all sparing the cortex—to mention only a few. As a clinical example, Sakel cites the case of a patient who ceased having hallucinations "just before the development of coma." Since coma is by definition a state of unconsciousness, it does not seem to me necessary to drag in this cumbersome explanation to account for the disappearance of a conscious phenomenon like hallucination as coma comes on. The author took "the risk of getting involved in mythology" (to use his own words) and succeeded in doing so. At present the clinical descriptions of progressive nervous disintegration during increasing hypoglycemia and of the reintegration after treatment are about as close as one can come to a theoretical conception of what is happening in the brain. Certainly something important is going on that improves the mental state of patients with dementia praecox. Nevertheless the treatment is not yet proved to be anything more than palliative, and there is some reason to believe that it may be causing permanent damage to the brains of patients who might spontaneously recover.

EPILEPSY

Electro-encephalography is proving to be useful in neurology, especially in the diagnosis of epilepsy.³² At the meeting of the American

32 Gibbs, F. A., Lennox, W. G., and Gibbs, E. L. Electro-Encephalogram in Diagnosis and in Localization of Epileptic Seizures, *Arch. Neurol. & Psychiat.* 36:1225-1235 (Dec.) 1936.

Psychiatric Association in May Lennox³³ described epilepsy as "cerebral dysrhythmia," meaning that sudden storms of irregular impulses spread across the brain of the epileptic person, giving rise to irregular waves on the electrical record Jasper,³⁴ however, read a paper giving evidence that these waves are not so much a matter of dysrhythmia as of "hypersynchronism," his idea being that many small waves come together and by their unison make the large abnormal waves seen in epilepsy Be that as it may, the instrument for recording cerebral waves is now a useful diagnostic tool, for even between clinical attacks of grand mal or petit mal there are many "larval attacks" These can be picked up on the electro-encephalogram, and they add greatly to one's security in making a diagnosis of epilepsy, for the histories are often not reliable and waiting to observe an attack is usually fruitless Gibbs is using the records to control treatment

Penfield,³⁵ after many years of work on the surgical treatment of epilepsy, has published the results in seventy-five cases His technic is an improvement of that originally described by Foerster,³⁶ it consists of meticulous history-taking and neurologic examination, careful encephalography, with an incision in the arachnoid space and ventricles, and observation of a seizure if one can be induced by hyperventilation or hydration With all these data in hand a decision is made as to the advisability of exploratory craniotomy If the operation is performed, a bone flap is turned down, and the brain is inspected for lesions and explored with a stimulating electrode for a trigger point, that is, a point of low threshold from which a weak stimulus will precipitate a convulsive attack Scars and adhesions that are found may be removed by clean dissection Trigger points may be excised if not too near the motor cortex or speech centers The technic is long and tedious and must be exquisitely carried out, otherwise more harm than good will be done The results are encouraging, 32 per cent of the seventy-five patients with epilepsy were free from attacks after craniotomy, and 23 per cent were improved

33 Gibbs, F A , Gibbs, E L , and Lennox W G Epilepsy A Paroxysmal Cerebral Dysrhythmia, Arch Neurol & Psychiat to be published

34 Jasper, H H , Hawke, W A , and Nichols, I C Localized Brain Potentials in the Convulsive Disorders, to be published

35 Penfield, W Epilepsy and Surgical Therapy, Arch Neurol & Psychiat **36** 449-484 (Sept) 1936

36 Foerster, O , and Penfield, W Der Narbenzug am und im Gehirn bei traumatischer Epilepsie in seiner Bedeutung für das Zustandekommen der Anfälle und für die therapeutische Bekämpfung derselben, Ztschr f d ges Neurol u Psychiat **125** 475-572, 1930

Book Reviews

Clinical Laboratory Diagnosis By Samuel Levinson, M S, M D, and Robert P MacFate, Ch E, M S Price, \$9.50 Pp 877, with 144 engravings and 13 plates, 5 in color Philadelphia Lea & Febiger, 1937

Among the recent publications dealing with clinical laboratory diagnosis, this book is noteworthy and unusual because each subject discussed is prefaced by a brief review of the anatomy, physiology and chemistry pertaining to the understanding of normal and abnormal findings. The subject matter is divided so as to deal with organs or systems by chapters, and each chapter contains only the simplest of essential technics, with the clinical significance of the findings pertinent thereto presented fully.

The first four chapters of the book deal with the examination of the secretions and excretions of the gastro-intestinal tract and include biochemical and pathologic, in addition to clinical microscopic, methods. Various technics are described for eliciting information regarding the status of the function of the various organs of each system, as well as demonstrating any lesion that may be present.

Chapter V discusses metabolism, with an introductory review of carbohydrate, nitrogen, fat and organic acid metabolism and a description of one method of estimating the basal metabolism. An account of the various dextrose tolerance tests and a few pertinent remarks on the acid-base equilibrium of the body also are given.

The chemical analysis of the blood is considered in chapter VI. This chapter is comprehensive and is an improvement over similar portions of other texts of this type. For each procedure the first paragraph outlines the principle of the method employed, thus tending to clarify the technic for readers not well informed in biochemistry.

Chapters VII and VIII, after a general consideration of the anatomy and function of the kidney, outline various methods of determining the normal and pathologic functioning of this organ, in addition to the chemical analysis of the urine. The authors have included tables of the various findings characteristic of the different forms of Bright's disease as well as of the inflammatory diseases of the kidney.

The section on hematology includes the routine and special procedures which are necessary for determinations of the quantitative and qualitative changes in all the formed elements of the blood. The latter part of chapter IX deals with a classification of the diseases of the blood and is clear, up-to-date and comprehensive.

Chapter X, the heading of which is "Immunology and Serology," deals chiefly with the Wassermann, Kahn and Kline tests for syphilis and the agglutination and precipitin tests for typhoid, tularemia and undulant fever. The examination of cerebrospinal fluid, with indications and contraindications for spinal puncture, the technic of spinal puncture and the interpretation of the findings, is dealt with in chapter XI.

As in all books of this type, one chapter is devoted to general bacteriology. Chapter XII of this text includes general bacteriologic technics, preparation of mediums, and stains and staining methods, which are of more interest to the laboratory worker than to the clinician.

The normal and pathologic findings for the sputum, with the routine procedures, including the typing of pneumococci by various methods and the findings characteristic of various pulmonary diseases, are given in chapter XIII. Cutaneous tests and other biologic examinations, including the hormone test for pregnancy, with the clinical significance of each, are considered in chapter XIV. Chapter XV is a resumé of the preceding portions of the text as applied to pediatrics and is a valuable asset to the book.

The remainder of the book, chapters XVI to XVIII, which is devoted to the analysis of milk and water, histologic technic, legal medicine and toxicology, is not directly pertinent to clinical pathology but is of marked assistance to persons engaged in clinical laboratory work. The appendix, which gives an outline for a course in clinical pathology, is of interest only to teachers of that subject.

The text, as a whole, because of its arrangement, is clear and brief, yet with no sacrifice of completeness, thus presenting a subject in terms easily understandable to the student and general practitioner as well as the specialist.

Diseases of the Respiratory Tract Eighth Annual Graduate Fortnight of the New York Academy of Medicine. Price, \$5.50. Pp 406, with 56 illustrations. Philadelphia: W. B. Saunders Company, 1936.

In presenting this symposium on respiratory diseases the Graduate Fortnight has accomplished its purpose—to select a “subject of outstanding importance in the practice of medicine and surgery” and to present it from as many angles as possible. In the twenty presentations practically every important aspect of respiratory disease is touched on, including allergy, the common cold, diseases of the sinuses, laryngeal, tracheal and bronchial disorders, bronchoscopy, bronchiectasis, influenza, chronic pneumonitis, pneumonia in childhood, immunology, evolution and surgery in tuberculosis, pneumoconiosis, emphysema, empyema, pulmonary tuberculosis and embolism, atelectasis and related conditions, carcinoma of the lung, and mediastinal diseases. The list of authors is impressive.

As with all works of multiple authorship, there are wide variations in the worth, thoroughness and clarity of each section. The sketchiness of the section on emphysema is an example. In the section on diseases of the larynx, trachea and bronchi an attempt to include all diseases of importance in a limited space reduces the context to the monotonous outline form of a compend and leaves no central thought with the reader. However, sections such as those on bronchiectasis and the evolution of pulmonary tuberculosis impart to the reader fewer concepts, but they are interestingly presented and leave a lasting impression.

The sections stressing pathogenesis and pathologic physiology, such as those on pulmonary tuberculosis by Miller, massive collapse by Henderson and immunity in tuberculosis by Rich, are ideal for the type of audience sought. A greater allotment of time and space to these presentations would add considerably to the value of the volume. There is at times some overlapping, which makes for smooth transition from one aspect of disease to another, but for the most part it is unnecessary.

The reader will become irked at times by the elementary nature of some sections but will be gratified in other sections by the authoritative summarization of the recent advances in respiratory diseases.

Les abcès du foie By P. Huard and J. Meyer-May. Price, 65 francs. Pp 390, with 98 illustrations. Paris: Masson & Cie, 1936.

Huard and Meyer-May present a discussion of hepatic abscess which includes a study of the medical literature and personal observations in 150 cases. They divide their material into eleven chapters on general statistics, surgical anatomy, etiology, pathogenesis and pathologic anatomy, symptoms and clinical forms, clinical differential diagnosis, hepatic puncture, roentgenography and roentgen surgery of hepatic abscess, geographic survey of the treatment of hepatic abscess, medical treatment and surgical treatment. At the end of the monograph the authors include 174 brief histories of cases, 43 autopsy reports and an extensive bibliography.

The subject in each chapter is discussed clearly and carefully. The correlation of etiology, anatomy and pathogenesis with the clinical manifestations of the disease is well done. The discussion of the technic and use of hepatic puncture for biopsy, exploration and injection of iodized poppy-seed oil is clearly presented from a practical standpoint. The authors doubt that all sterile abscesses of the liver should be considered amebic unless proved by microscopic demonstration of amebas. They cite the autopsy studies of Joyeux in nearly 100 cases of hepatic

abscess of Tonkin in which no amebas were encountered. Huard and Meyer-May, however, believe that pus-forming amebas deserve more etiologic consideration than is usually given. The authors have not attempted to simplify the clinical picture of hepatic abscess for diagnosis. They, like most French clinicians, probably have divided the disease into too many unnecessary clinical forms, thus complicating rather than simplifying the clinical diagnosis.

As a whole the monograph is clear and thorough. Although it presents nothing essentially new, it emphasizes the clinical significance of the disease and renders aid to the medical profession by presenting a comprehensive source of information on abscess of the liver.

The Management of the Pneumonias By Jesse G. M. Bullock, M.D., Clinical Professor of Medicine, New York University College of Medicine, and Director, Littauer Pneumonia Research Fund. Price, \$8.50. Pp. 525, with 142 illustrations and 88 tables. New York: Oxford University Press, 1937.

In this book the whole story of pneumonia is told clearly and forcibly. The clinical picture of pneumonia first is dealt with, and then are described the laboratory and roentgen methods employed in diagnosis. The manner in which typing of sputum, blood cultures and agglutination tests should be carried out and the significance of these laboratory tests are particularly well presented.

The second section of the book deals with general principles of treatment. This also makes interesting reading for the clinician. It is thoroughly up-to-date, for even the therapeutic value of sulfanilamide and its derivatives is mentioned. The question of treatment is taken up sanely, and the author evaluates therapeutic results in terms of his own experience, which makes what he says all the more pertinent. "Diathermy has not been associated with a reduction in mortality among bacteremic patients." "We did not find that pneumothorax benefited blood invaded patients, the group where therapeutic effort is really needed most." "We now use no whiskey or alcohol in the treatment of the pneumonias, regardless of habit."

All the details of treatment are described meticulously: how to put on a thoracic swathe properly, how to control dehydration and how to administer hypertonic solutions of sugar. Treatment with oxygen receives prolonged discussion, and the various means by which oxygen may be administered effectively are well illustrated. Serum therapy, of course, is fully discussed.

The prognosis of pneumonia is considered in a relatively short chapter. The final chapter deals with the complications of pneumonia and their management.

On the whole the book is readable from beginning to end and is one of the most valuable and comprehensive reviews of pneumonia that have been published in many years.

La vésicule biliaire et ses voies d'excrétion By M. Chiray, M.D., and I. Pavel, M.D. Second edition. Price, 120 francs. Pp. 863, with 203 illustrations. Paris: Masson & Cie, 1936.

The first edition of this book, published in 1926, was so well received that Chiray and Pavel were prompted to write the present edition, which is a complete revision of the first. Old chapters have been modified and new ones added. Many unnecessary discussions have been eliminated and more complete ones presented, especially the discussions on physiology and radiology. The section devoted to the radiologic aspects of diseases of the gallbladder and the biliary tract was written by A. Lomon.

The book is divided into five parts, which include the following: anatomy, histology and physiology, methods of examination, gallbladder syndromes, diseases of the gallbladder, and medical and surgical treatment. The discussions are thorough, covering the important work of European and American observers interested in the functions and diseases of the gallbladder and biliary ducts. The authors also present their personal observations and ideas on various aspects of the subject. At the end of each chapter there is a rather exhaustive bibliography, which

includes only articles published since 1926, when the first edition appeared. There are many enlightening figures and illustrations. Complete indices by author and by subject are included.

The reviewer recommends the book to the clinician. It is a thorough, up-to-date presentation of diseases of the gallbladder and the biliary tract. It is lucidly and exhaustively written and should serve, at least, as a good reference book.

Diseases of the Nails. By V. Pardo-Castello. Price, \$3.50. Pp. 377. Springfield, Ill., Charles C. Thomas, Publisher, 1936.

This excellent monograph by a dermatologist particularly well qualified in the field is the only comprehensive survey of its kind in the English language. Dr. Pardo-Castello capably fulfills his purpose of making a complete yet simple summary of the subject. The first chapter deals with anatomy and histology and includes the newer concepts of the circulation of the nail bed and the chemical composition of the nails. The pathologic changes in the nails in general are outlined in the second chapter, which includes a table of the frequency of disorders of the nails. The following four chapters are concerned with disorders peculiar to the nails, onychodystrophies, ungual manifestations of dermatoses and of systemic diseases and congenital diseases of the nails, thus roughly classifying the types of changes in nails. Under each individual subdivision the most effective therapeutic measures are given clearly. Roentgen treatment, with its indications and dosage, is discussed briefly in the last chapter. An addendum includes a tabulation of occupations in which diseases of the nails are common and a list of ungual symptoms due to particular poisons. The book is supplemented by numerous good illustrations and a comprehensive bibliography.

This small book is unusually complete and has a definite place in any medical library as a reference work; it will be particularly valuable to most dermatologists, to whom the terminology and classification of this subject have always been somewhat confusing.

Recent Advances in Allergy. By George W. Brav. Third edition. Price, \$5. Pp. 484. Philadelphia. P. Blakiston's Son & Co., 1936.

This is a comprehensive review of the present knowledge of allergy, in which the literature on the subject is reviewed and discussed and nearly three thousand references are listed. The manifestations of allergy are considered individually, and the etiology, pathology, diagnosis and treatment are ably presented. The common allergic reactions are treated at length, and those which are less common are described and discussed in less detail.

The general form of the third edition remains essentially the same as that of the previous editions, although the older material has been revised and condensed and certain parts have been rewritten. In the chapter on distribution of pollens, the hay fever-producing plants of the British Isles have been classified, and their relative importance in causing hay fever has been considered. Except for this chapter, which deals with the flora of the British Isles only, the subject of allergy in general is well covered.

This book is a practical and conservative presentation of the present knowledge of allergy, and the reviewer considers it worthy of a place in the library of any one interested in the diagnosis and treatment of this condition.

Zehn Vorlesungen über Kymographie. By Pleikart Stumpf. Price, 870 marks. Pp. 112, with 80 illustrations and 1 celluloid grid. Leipzig. Georg Thieme, 1937.

This little volume is an abstract of the large book by Stumpf, which was reviewed in these columns recently. For the ordinary physician who is not a specialist this brief compendium serves admirably to acquaint him with the essential facts of roentgenkymography. Those who are interested in more details are referred to the review of the larger work.

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